Non-cardiac chest pain : the role of panic disorder and depression

Non cardiac chest pain

THE ROLE OF PANIC DISORDER AND DEPRESSION

Petra Kuijpers

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PART C | *biological issues*

1

1 |

Chest pain: a fearful experience

INTRODUCTION

Panic disorder (PD) with or without comorbid depression is common among patients presenting with chest pain to an Emergency Department (ED) or First Heart Aid (FHA) [1-3]. Each year more than 6 million patients in the United States present to ED's with chest pain or other symptoms suggestive of myocardial ischemia [4]. A large part of this group is hospitalised, but a cardiac etiology is found in less than one-third [5].

Prevalence of PD driven chest pain ranges between 16% and 75%, depending on the population and screening methods [3]. According to the Diagnostic and Statistical Manual IV (DSM IV) panic attacks are defined as sudden spells of unidentified feelings consisting of at least 4 out of 13 symptoms [6]. The symptoms are listed in table 1. In order to make a diagnosis of PD, additional criteria are the unexpected nature of the attacks, followed by at least one month of fearful expectation or concern about the consequences of the attack [7]. These attacks can mimic anginal complaints.

PD has important consequences for the health care system, leading to frequent hospital admissions and unnecessary diagnostic investigations with the risk of iatrogenic complications [8]. Also quality of life of non cardiac chest pain patients with PD is markedly decreased [9].

PD often remains unrecognized as patients themselves may present with primarily somatic symptoms such as chest discomfort, rather than psychological symptoms such as fear [10]. Therefore, there is an important clinical need for changes in our approach to care for patients presenting with chest pain, with easier access to routine psychological assessment and use of multidisciplinary help [11]. Development of specific diagnostic tools is essential for this large population in order to correctly diagnose the cause of the somatic complaints and referral to the right doctor for psychiatric and/or psychological treatment when needed.

TABLE 1 | Symptoms of a panic attack [6]

1.	Shortness of breath (dyspnea) or smothering sensations
2.	Dizziness, unsteady feelings, or faintness
3.	Palpitations or accelerated heart rate
4.	Trembling or shaking
5.	Sweating
6.	Choking
7.	Nausea or abdominal distress
8.	Depersonalisation or derealisation
9	Numbness or tingling sensations (paresthesias)
10.	Flushes or chills
11.	Chest pain or discomfort
12.	Fear of dying
13.	Fear of going crazy or losing control

In this thesis, the subject of non cardiac chest pain in Emergency Department or First Heart Aid populations is divided into three parts:

- General issues
- Diagnostic issues
- Biological issues

GENERAL ISSUES

This part consists of three chapters. The first two are in Dutch, as we started with reviewing literature on the subject of non cardiac chest pain and the role of PD and depression. Subsequently, we performed a pilot study at the First Heart Aid (FHA) of the University Hospital Maastricht. When we realised the magnitude of the problem, it was decided to publish further studies in international journals. This clinical problem is not unique for Dutch cardiologists, but daily practice of every cardiologist. The main part of the thesis is, therefore, in English.

Chapter 2 is a general introduction into the significance and magnitude of the problem in patients with cardiac complaints. It describes what PD is and its impact on health care consumption, costs, quality of life and prognosis [1]. Chapter three describes a pilot study performed at the FHA of the University Hospital Maastricht, to investigate the magnitude of PD driven non cardiac chest pain in our own hospital [2] .

Chapter 4 describes the effects and importance of PD in patients with an Implantable Cardioverter Defibrillator (ICD), as well as the result of psychiatric treatment on serious cardiac arrhythmias [12].

DIAGNOSTIC ISSUES

The large number of potential patients presenting to an ED stimulated us to look for a simple and validated screening instrument. Until now, the Hospital Anxiety and Depression Scale (HADS), a self rating questionnaire consisting of 14 items which takes only a few minutes to fill out, was not validated for this specific population. In Chapter 5 a study is described which validates the HADS as a screening instrument for PD and/or depression in patients presenting with non cardiac chest pain in an ED setting [13].

Chapter 6 presents a study on the role of Type D personality in non cardiac chest pain patients. It has been shown that type D personality (characterized by negative affectivity and social inhibition) plays a prognostic role in cardiac patients. The incidence of Type D personality has not been studied in patients with PD. This chapter investigates the prevalence and effects of Type D personality in PD driven chest pain.

Chapter 7 evaluates the diagnostic value and safety of the 35% CO_2 challenge test in this specific population. The carbon-dioxide challenge test is an established diagnostic test for PD in physically healthy patients [11-13]. However, this test has not been used in somatically ill patients or patients suffering from PD presenting primarily with somatic symptoms. In chapter 7, we present a study validating the CO_2 challenge test in this specific patient group.

BIOLOGICAL ISSUES

As stated earlier, there is a link between cardiology and psychiatry ("the heart and the brain"). Several biological substances have been found to play a role in anxiety as well as

depression. In this part of the thesis, we investigated blood platelet factors and polyunsaturated fatty acids (PUFA's) in patients with and without psychopathology.

Chapter 8 describes a study performed in patients following a first myocardial infarction, one group with depressive symptoms and the other group without depressive symptoms. We studied Platelet Factor 4 and Beta-thromboglobulin activity in these two groups [14].

Chapter 9 describes the same platelet activity substances, as well as serotonin and sCD40L in patients with non cardiac chest pain suffering from PD and/or depression as well as a control group.

Chapter 10 investigates the role of polyunsaturated fatty acids (PUFA's) in this specific population.

Chapter 11 gives the main conclusions of this thesis and presents a general discussion of the results with implications for future research.

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PART A

general issues

2 |

Paniekstoornis bij patiënten met pijn op de borst en palpitaties:
een onvoldoende onderkend verband

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ABSTRACT

Panic disorder in patients with chest pain and palpitations: an insufficiently recognized connection

- The prevalence of panic disorder in patients who present with chest pain or palpitations to a First Heart Aid setting varies in literature between 0% and 59%.
- In a high percentage of cases, the cardiologist does not recognize panic disorder in patients who present initially with chest pain or palpitations. Patients with panic disorder have a large and ongoing medical consumption.
- A selective serotonin reuptake inhibitor (SSRI) and/or cognitive therapy appear to be good treatment of panic disorder in patients who present initially with chest pain or palpitations.
- A CO_2 challenge test elicits the symptoms in patients with panic disorder with high

sensitivity and specificity but this test has not been validated in patients who present initially with chest pain or palpitations and in whom the diagnosis 'panic disorder' is not yet established.

SAMENVATTING

- Paniekstoornissen komen in de literatuur voor bij 0-59% van de patiënten die zich met pijn op de borst en/of palpitaties melden bij de cardioloog
- Miskenning van paniekstoornissen en/of depressie door de cardioloog bij patiënten die zich met pijn op de borst en/of hartkloppingen presenteren is groot. Patiënten met een paniekstoornis doen een voortdurend en groot beroep op de gezondheidszorg.
- Vooralsnog lijkt behandeling met een selectieve serotonine heropnameremmer (SSRI) en/of cognitieve therapie de voorkeursbehandeling te zijn voor een paniekstoornis bij patiënten die zich melden met pijn op de borst en/of palpitaties.
- Bij patiënten met een paniekstoornis kunnen met een CO_2-provocatietest de symptomen met hoge sensitiviteit en specificiteit worden opgeroepen, maar deze test is niet onderzocht bij patiënten die zich melden met pijn op de borst of palpitaties en die nog niet bekend zijn wegens een paniekstoornis.

INLEIDING

Patiënten met pijn op de borst of hartkloppingen vormen een groot deel van de patiënten die zich bij de cardioloog melden. Bij velen blijkt er geen cardiale genese te zijn. Zij hebben snel het gevoel 'aanstellers' te zijn, het zich te verbeelden of 'het tussen de oren' te hebben.

In de dagelijkse praktijk heeft meer dan de helft van de cardiologische polikliniekpopulatie en ongeveer eenderde deel van patiënten op de Eerste Harthulp klachten van pijn op de borst of hartkloppingen waarvoor na analyse geen cardiale oorzaak kan worden vastgesteld. In een aanzienlijk deel van dergelijke gevallen berusten de klachten op een paniekstoornis [1-4].

Reeds in 1871 beschreef Da Costa het 'irritable heart syndrome', hetgeen later het 'syndroom van Da Costa' werd genoemd. Dit syndroom kwam ten tijde van de Eerste Wereldoorlog veel voor bij soldaten en werd 'soldatenhart' genoemd [5-6]. Termen die in de loop van de tijd gebruikt zijn voor klachten van pijn op de borst waarbij geen cardiale afwijking

TABLE 1 | **Symptomen van paniekaanvallen en criteria voor paniekstoornis (DSM-IV-criteria)***

1.	hartkloppingen, hartbonzen of een snel kloppend hart
2.	transpireren
3.	trillen of beven
4.	kortademigheid of het gevoel te stikken
5.	naar adem snakken
6.	pijn of een onaangenaam gevoel op de borst
7.	misselijkheid of buikklachten
8.	duizeligheid, gevoel van onvastheid of flauwte
9.	een gevoel van vervreemding of van onwerkelijkheid
10.	angst om de controle te verliezen of gek te worden
11.	angst om dood te gaan
12.	gewaarwording van doofheid of tintelingen
13.	het plotseling warm of koud krijgen

**Voor de diagnose 'paniekstoornis' zijn tenminste 4 van deze symptomen nodig, die bovendien acuut dienen te ontstaan en binnen 10 minuten hun piek moeten bereiken. Bovendien moeten er tenminste 2 aanvallen zijn geweest en dient de patiënt zich gedurende tenminste een maand zorgen te hebben gemaakt over het al dan niet opnieuw optreden van een aanval, hetgeen leidt tot vermijdingsgedrag en isolatie.*

kon worden gevonden, zijn onder andere 'folie cardiaque', 'angstneurose', 'neurocirculatoire asthenie' en 'hyperventilatie' [6-7].

In dit artikel bespreken wij diagnostiek, prevalentie, beloop, etiologie, provocatietests, behandelingsmogelijkheden alsmede kostenaspecten inzake pijn op de borst of palpitaties die berusten op een paniekstoornis.

DIAGNOSTIEK VAN PANIEKSTOORNISSEN

Paniekstoornissen komen bij 1,5-2,3% van de volwassen populatie voor en gaan gepaard met belangrijke functionele beperkingen [8].

Volgens de DSM-IV [9] is een paniekstoornis een abrupt optredende korte periode van intense angst of onwelbehagen, waarbij zich tenminste 4 of meer symptomen voordoen

die acuut ontstaan en binnen 10 minuten hun piek bereiken. De symptomen zijn voornamelijk vegetatief van aard, zoals vermeld in tabel 1. Tevens moeten er tenminste 2 aanvallen zijn geweest en heeft de patiënt zich gedurende tenminste één maand zorgen gemaakt over het al dan niet opnieuw optreden van een aanval, hetgeen leidt tot vermijdingsgedrag en isolatie.

Risicofactoren beschreven voor paniekstoornis zijn: jong volwassen leeftijd en vrouwelijk geslacht; vrouwen hebben 2 maal vaker een paniekstoornis dan mannen [8]. Bij vrouwen gaat de paniekstoornis vaker gepaard met agorafobie met na remissie een grotere kans op recidieven dan mannen [10]. Er zijn inmiddels aanwijzingen dat paniekstoornis mede erfelijk bepaald is [8, 11]. De prevalentie van paniekstoornis bij eerstegraadsfamilieleden (ouders, broers, zussen) ligt tussen de 15 en 20%; ongeveer 10 keer zo hoog als verwacht [12].

Depressie en paniekstoornis worden vaak als comorbiditeit bij elkaar gezien. Patiënten die zich presenteren met een depressie hebben in 30% van de gevallen een paniekstoornis [13]. Ten tijde van presentatie hebben patiënten met een paniekstoornis in ongeveer 30% van de gevallen ook een depressie. Bij paniekstoornis is de totale prevalentie gedurende het gehele leven van een comorbide depressie maar liefst 68% [13]. Het blijft daarom de vraag of paniekstoornis en depressieve stoornis twee relatief onafhankelijke stoornissen zijn dan wel verschillende uitingsvormen van een en hetzelfde syndroom, met één onderliggende oorzaak.

Diagnostiek van paniekstoornis op de eerste hulp of bij een cardiologische populatie

Patiënten met paniekstoornis melden zich vaak bij een polikliniek Cardiologie of een Eerste (Hart) Hulp. Zij presenteren zich met pijn op de borst of palpitaties. Indien er geen cardiale genese is, maar wel de diagnose 'paniekstoornis' wordt gesteld, lijken deze patiënten een ander symptomencomplex te hebben dan andere paniekpatiënten, bij wie niet zozeer cardiale klachten als wel angstklachten op de voorgrond staan. Bij het cardiale symptoomcomplex staan niet zozeer angstklachten centraal, maar het tweede kernsymptoom: onwelbehagen; men spreekt dan wel van 'paniekstoornis zonder angst' ('non fearful panic disorder') [14-16]. Met name wanneer angstklachten niet op de voorgrond staan en er niet specifiek wordt doorgevraagd naar andere symptomen van paniekstoornis, wordt herkenning ervan bemoeilijkt.

De herkenning van een paniekstoornis door cardiologen is gering: 2% [3]. Ook andere onderzoeken tonen aan dat slechts door een zeer beperkt deel van de artsen werkzaam op

een Eerste Hulp een psychiatrisch probleem of een psychosociale oorzaak voor de klachten genoemd wordt; het percentage varieert tussen de 1 en 9 [17]. In een recentelijk door ons uitgevoerd pilotonderzoek (elders in dit nummer afgedrukt) was de herkenning 13% [18].

PREVALENTIE EN BELOOP VAN PANIEKSTOORNISSEN BIJ CARDIOLOGISCHE PRESENTATIE

De literatuur geeft sterk wisselende schattingen over de prevalentie en incidentie van klachten van paniekstoornis. Ongeveer 30% van de nieuwe patiënten die zich bij een cardioloog melden met pijn op de borst, heeft normale kransslagaders bij angiografisch onderzoek [15]. Bij patiënten met pijn op de borst en normale coronairvaten varieert het percentage paniekstoornis tussen de 22 en 59 [1, 4, 5, 7, 16, 19]. Bij patiënten met bewezen coronarialijden variëren de gevonden percentages van paniekstoornissen nog meer tussen de diverse onderzoeken: van 0 tot 53 [1, 3, 5, 16, 20]. Deze variatie hangt mede samen met verschillende screeningsmethoden om de diagnose 'paniekstoornis' te stellen alsmede met bias in de selectie van patiëntengroepen.

Voor wat betreft het beloop van klachten, gezondheidszorgconsumptie en cardiologische prognose is het volgende bekend. Pijn op de borst gaat samen met frequent gebruik van gezondheidszorgvoorzieningen: patiënten bezoeken vaak huisartsen, specialisten, poliklinieken en EHBO-posten. Patiënten die na onderzoek geen cardiale afwijkingen blijken te hebben, blijven in meerderheid klachten houden [3, 5, 19].

Wat betreft beperkingen op het gebied van fysieke inspanning en het gebruik van medische voorzieningen, hebben patiënten met pijn op de borst en normale coronairvaten en paniekstoornis de slechtste prognose [4, 5, 7, 21]. Er is nauwelijks een verandering in klachtenpatroon en beperkingen gedurende uitgebreide follow-up tot 10 jaar [4]. Een recent Brits onderzoek toonde aan dat dit ook geldt voor patiënten die zich met hartkloppingen presenteren [22]; bij de meesten kon geen cardiologische diagnose worden gesteld. Geruststellen door het mededelen dat er geen medische afwijking was te vinden en dat de patiënt een normaal leven kon leiden, had slechts beperkt effect. Na 18 maanden voelde 33% van de patiënten zonder cardiale afwijking zich hetzelfde (met evenveel klachten); 10% voelde zich nog slechter.

Dit werd ook aangetoond door een recent Nederlands onderzoek van Van Peski-Oosterbaan et al. [23], die vonden dat 1 jaar na presentatie bij de cardioloog van onverklaarde klachten van pijn op de borst in 72% van de gevallen deze klachten nog aanwezig waren;

na 2 jaar was dit percentage nog steeds 56. Echter, de vraag is of al deze klachten toe te schrijven zijn aan paniekstoornis, aangezien in dit onderzoek geen paniekstoornisdiagnostiek werd verricht.

Wat betreft de cardiologische prognose zijn er in de literatuur conflicterende data. Alhoewel langetermijnonderzoeken hebben aangetoond dat deze patiëntengroep een uitstekende prognose heeft wat betreft cardiale morbiditeit en mortaliteit [4, 24], zijn er andere onderzoeken die hebben aangetoond dat angst een risicofactor is voor het ontstaan van cardiale aandoeningen [25]. Sommigen vonden dat fobische angst een sterke voorspellende variabele is van plotse hartdood met een drievoudig verhoogd risico [26]. Ook hebben patiënten met paniekstoornis een licht verhoogde bloeddruk en een hogere submaximale hartslag bij inspanningstests, vergeleken met controlepersonen [27], en een verhoogde serumcholesterolconcentratie vergeleken met depressieve patiënten en normale controlepersonen [28].

Paniekpatiënten hebben meerdere leefgewoonten die kunnen predisponeren tot harten vaatziekten, zoals roken of overmatig alcoholgebruik, en vermijden vaker lichamelijke inspanningen, omdat dit een verhoogde hartslag en een paniekaanval tot gevolg kan hebben [29].

Er blijkt een grote samenhang te zijn tussen paniekstoornis en somatisatiestoornis [30, 31]: 89% van de paniekpatiënten presenteerde zich aanvankelijk met een of twee somatische klachten [30], een van de oorzaken waardoor het missen van de paniekstoornis soms jaren kan standhouden. Cardiale symptomen behoren, samen met gastro-intestinale en neurologische klachten, tot de gebruikelijkste presentatievorm.

ETIOLOGIE VAN PANIEKSTOORNIS

Een exacte oorzaak of keten van oorzakelijke factoren van paniekstoornis is onbekend. Tijdens een paniekaanval treedt acute hyperventilatie op. Experimenteel onderzoek toont aan dat hyperventilatie op zich geen afdoende oorzaak of voorwaarde voor paniekaanvallen is. Een van de belangrijke respiratoire theorieën is de theorie inzake 'vals verstikkingsalarm' van Klein [32]. Deze beweert dat een paniekaanval veroorzaakt wordt door een vals alarm van een hypothetische verstikkingsmonitor in het centrale zenuwstelsel. Deze monitor zou overgevoelig zijn voor lactaat en kooldioxide.

Ook het lactaatsysteem wordt in verband gebracht met paniekstoornis. Het exacte mechanisme hiervan is nog steeds onduidelijk. Hyperventilatie en het parasympathische

zenuwsysteem lijken betrokken te zijn bij lactaatprovocatie. Centrale serotoninedisregulatie is zowel bij paniekstoornis als bij depressieve stoornissen aangetoond. Antidepressiva met overwegend effect van serotonine-heropnameremming zijn geregistreerde medicamenten bij de paniekstoornis. Dit betreft zowel tricyclische antidepressiva, te weten clomipramine en in mindere mate imipramine, alsook de selectieve serotonineheropnameremmers (SSRI's) paroxetine, fluoxetine, fluvoxamine, citalopram en sertraline.

PANIEKPROVOCATIETESTS

Op basis van de diverse theorieën zijn er ook verschillende provocatietests ontwikkeld [33]. Diverse stoffen blijken angst en zelfs paniekachtige aanvallen op te kunnen wekken. Zo is bij toediening van de serotonine-agonisten metachloorfenylpiperazine en fenfluramine en van de serotoninevoorlopers tryptofaan en 5-hydroxytryptofaan een angstreactie beschreven.

Natriumlactaat en CO_2 provoceren eveneens paniekaanvallen. Het paniekprovocerende effect van deze twee laatste stoffen is echter aantoonbaar specifiek. Alleen paniekpatiënten en gepredisponeerde individuen zijn gevoelig voor een lactaatinfuus of CO_2-inhalatie [34].

Een enkelvoudige inhalatie van een mengsel van 35% CO_2 en 65% O_2 wekt bij voor paniekstoornis gevoelige personen een vluchtig gevoel van angst op, met duidelijke neurovegetatieve symptomen, gelijk te stellen aan het ontstaan van een paniekaanval [35]. Deze reactie blijft achterwege bij zowel gezonden als individuen met andere angststoornissen. De sensitiviteit van deze test is 91%, de specificiteit 50%, de voorspellende waarde van een positieve uitslag 84%, die van een negatieve 64% [36].

Binnen de experimentele psychiatrie zijn er reeds lang CO_2-provocatietests gedaan, echter, vooral bij patiënten met een paniekstoornis en niet bij patiënten die zich primair melden met pijn op de borst en vervolgens een paniekstoornis blijken te hebben.

Er lijkt in deze specifieke populatie behoefte te zijn aan een provocatietest om de volgende redenen: simpele gerichte vragen kunnen een indicatie geven over de eventuele aanwezigheid van een psychiatrische diagnose, maar vaak overtuigt dat de patiënt niet. De CO_2-provocatietest veroorzaakt bij patiënten de initiële aanmeldingsklacht (indien deze door paniekstoornis werd veroorzaakt) en dat legt ook voor hen de relatie tussen paniekstoornis en pijn op de borst of hartkloppingen. Dit kan verwijzing naar de psychiater acceptabel maken.

FINANCIËLE CONSEQUENTIES

Diverse onderzoeken hebben aangetoond dat gezondheidszorgkosten voor paniekpatiënten hoog zijn en dat behandeling van deze aandoening zou kunnen leiden tot een daling van de kosten alsmede een afname van bezoeken aan gezondheidszorgwerkers en ziekenhuisopnamen [37, 38].

In de VS schatte men bij 391 patiënten met een paniekstoornis de uitgaven aan poliklinische zorg op 3 miljoen dollar [37]; de gemiddelde geschatte uitgaven per paniekaanval waren 3339 dollar. Anderen berekenden de medische kosten een jaar vóór en een jaar ná effectieve behandeling voor een paniekstoornis bij 61 patiënten [38]. Door de behandeling daalde het aantal bezoeken aan huisartsen en specialisten van 313 naar 15 en het aantal bezoeken aan een Eerste Hulp van 75 naar 7. De ziekenhuisopnamen daalden van 3 met 22 verblijfsnachten naar nul. De totale kosten waren daardoor meer dan 34.000 dollar lager per patiënt.

BEHANDELING VAN PANIEKSTOORNISSEN

De behandeling van de paniekstoornis bestaat enerzijds uit de behandeling van de paniekaanval en anderzijds uit die van het vermijdingsgedrag en de sociale isolatie. Zowel farmacotherapie als cognitieve gedragstherapie is effectief gebleken. Beide behandelingen worden voorafgegaan door uitleg over de paniekstoornis en de niet-cardiale genese alsook over het voorkómen van vermijdingsgedrag. Soms is deze uitleg al voldoende om de frequentie van de paniekaanvallen en met name het herhaald zoeken van cardiologische hulp te verminderen.

Selectieve serotonineheropnameremmers

SSRI's en de overwegend serotonerg werkende tricyclische antidepressiva zijn effectief bij de behandeling van paniekstoornissen [39-44]. Van deze serotonerg werkende medicamenten zijn de SSRI's te prefereren, omdat deze in tegenstelling tot tricyclische antidepressiva geen klinisch relevante cardiale bijwerkingen hebben [45]. De laatste jaren zijn er diverse gerandomiseerde dubbelblinde placebogecontroleerde onderzoeken gedaan, waarbij de effectiviteit van een aantal SSRI's bestudeerd is bij psychiatrische patiënten met paniekstoornis [41, 42, 46-49].

De effectiviteit van clomipramine, fluvoxamine, paroxetine, fluoxetine, citalopram en

sertraline voor de behandeling van paniekstoornissen is aangetoond. Farmacologische behandeling met SSRI's en serotonerg werkende tricyclische antidepressiva kan aanvankelijk een toename van de paniekaanvallen geven, waarna er na 2-3 weken een afname optreedt. Tijdens de aanvankelijke toename van klachten kan gedurende 1 tot 2 weken een benzodiazepine worden voorgeschreven. Het maximale effect treedt op na 2-3 maanden behandeling. Benzodiazepinen zijn op zich niet effectief, behoudens alprazolam en clonazepam. Beide medicamenten geven verlichting op korte termijn, maar geven aanzienlijke sedatie en een potentieel gevaar voor afhankelijkheid in tegenstelling tot de serotonerg werkende medicamenten.

Cognitieve gedragstherapie

Cognitieve gedragstherapie is gericht op enerzijds de verkeerde interpretatie van de optredende vasovegetatieve klachten door de patiënt en anderzijds op het oefenen van blootstelling aan de angstwekkende situatie die de patiënt tracht te vermijden (bijvoorbeeld het alleen de straat opgaan). Geleidelijk treedt gewenning op en nemen de klachten af.

Het is echter de vraag of paniekstoornis met voornamelijk een cardiale presentatie dezelfde genese heeft als een niet-cardiaal gerelateerde paniekstoornis. Er zijn geen effectiviteitsdata met betrekking tot farmacologische of cognitieve therapie bij deze specifieke presentatievorm bekend.

CONCLUSIE

Paniekstoornis is, ook in Nederland [50], een frequent voorkomend, maar helaas veelvuldig miskend probleem bij patiënten die zich op een Eerste Harthulp melden met klachten van pijn op de borst of hartkloppingen die niet op een cardiale genese berusten. De herkenning van paniekstoornis als specifieke psychiatrische aandoening in een niet-psychiatrische setting is erg gering [3]. Indien deze klachten niet worden herkend als behorend bij paniekstoornis en niet als zodanig behandeld worden, treedt er over het algemeen een chronisch beloop op met een groot verbruik van gezondheidszorgvoorzieningen. Dit kan uitmonden in hoge gezondheidszorgkosten, een ernstige aantasting van de kwaliteit van leven en mogelijk een slechte prognose voor optreden van daadwerkelijke hart- en vaatziekten, en in psychiatrische comorbiditeit.

Vroege herkenning van een paniekstoornis, zowel door de cardioloog als door andere specialisten en door de huisarts, is dus essentieel. Uitleg over de aandoening aan de pa-

tiënt en de cardioloog alsmede een doelgerichte verwijzing naar de psychiater kunnen bijdragen tot een betere behandeling, hetgeen tot verbetering van de kwaliteit van leven en vermindering van productieverlies leidt en uiteindelijk resulteert in een kostenbesparing voor de gezondheidszorg.

Theoretisch gezien zou een CO_2-provocatietest bij vermoeden van paniekstoornis een mogelijkheid zijn om de diagnose te bevestigen en ook om de patiënt zelf te overtuigen dat de klachten op te roepen zijn, echter, hierover zijn bij deze specifieke patiëntengroep met cardiale verschijnselen nog onvoldoende gegevens. Mocht de test ook bij deze populatie een hoge sensitiviteit en specificiteit hebben, dan zou hij relevant kunnen zijn, ook voor de cardiologische praktijk. Ter vergelijking: ergometrie, binnen de cardiologie een van de meest gebruikte diagnostische tests, is ook een soort provocatietest, die zijn nut ruimschoots bewezen heeft.

Gezien de hoge comorbiditeit met andere psychiatrische aandoeningen alsmede het chronische beloop is een behandeling van paniekstoornis zeer aan te bevelen. Vooralsnog lijkt behandeling met een SSRI en/of cognitieve therapie de voorkeur te hebben. Een manier om het missen van de aandoening te voorkomen is om de mogelijkheid van paniekstoornis eerder in de differentiaaldiagnose op te nemen. Preoccupatie met een cardiale genese bij patiënten met pijn op de borst of palpitaties zou beschouwd kunnen worden als een 'folie cardiaque', niet alleen bij de patiënt, maar ook bij de dokter.

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Paniekstoornissen, pijn op de borst en palpitaties:
een pilotonderzoek op een Nederlandse Eerste Harthulp

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ABSTRACT

Panic disorder, chest pain and palpitations:
a pilot study at a Dutch First Heart Aid

Many panic disorders in patients in First Heart Aids with chest pain and palpitations without a cardiac origin of the complaints

Objective: To determine how many patients, presenting to a First Heart Aid (FHA) with chest pain or palpitations without a cardiac origin for their complaints, have a panic disorder and/or depression.

Design: Prospective and questionnaire investigation

Method: In 3 months (November 1st 1998-January 31st 1999) all patients presenting to the FHA of the University Hospital Maastricht, the Netherlands, and who were not admitted, were screened for the presence of psychopathology by means of a questionnaire, the 'Hos-

pital Anxiety and Depression Scale' (HADS). Patients scoring above 8 on the HADS with no cardiac cause for their initial complaint were interviewed using the 'Mini international neuropsychiatric interview' (MINI) to determine whether there was a panic disorder and/or a depressive episode.

Results: Of a total of 621 patients 251 met the inclusion criteria: 134 (53%) gave informed consent (72 (54%) men and 62 (46%) women, with a mean age of 55.9 (SD: 13.2; range: 23-84)). Of the 134, 77 had a HADS score ≥ 8; in 59 (30 men; 29 women) the MINI was carried out: in 49 (83%) panic disorder (n=45) or depression (n=4) was diagnosed. In 7/45 the cardiologist had diagnosed a psychiatric disorder ('hyperventilation').

Conclusion: In 83% of the patients who visited the Maastricht FHA with cardiac complaints but without a cardiac origin and who had a HADS score ≥ 8, panic disorder and/or depression was diagnosed.

SAMENVATTING

Doel: Vaststellen hoe vaak een paniekstoornis en/of depressie voorkomt bij patiënten die zich met klachten van pijn op de borst of hartkloppingen melden op een Eerste Harthulp (EHH) en bij wie er op dat moment geen cardiale genese voor deklachten kan worden gevonden.

Opzet: Prospectief enquêteonderzoek.

Methode: In 3 maanden (1 november 1998 – 31 januari 1999) werden alle patiënten die zich met pijn op de borst of palpitaties zonder cardiale genese op de EHH van het Academisch Ziekenhuis Maastricht meldden en vervolgens werden ontslagen, psychiatrisch gescreend door middel van een vragenlijst, de 'Hospital Anxiety and Depression Scale' (HADS). Indien de patiënt boven een vastgestelde grenswaarde van 8 scoorde en geen cardiologische genese van de klachten had, werd door middel van een gestructureerd psychiatrisch interview, de 'Mini international neuropsychiatric interview' (MINI), beoordeeld of er een paniekstoornis en/of depressie was.

Resultaten: Van een totaal van 621 patiënten voldeden 251 aan de inclusiecriteria: 134 (53%) gaven informed consent (72 (54%) mannen; 62 (46%) vrouwen, met een gemiddelde leeftijd van 55,9 jaar (SD: 13,2; uitersten: 23-84)). Van de 134 scoorden 77 ≥ 8 op de HADS; bij 59 (30 mannen; 29 vrouwen) van hen kon de MINI worden afgenomen: bij 49 (83%) werd paniekstoornis (n=45) en/of depressie (n=4) gediagnosticeerd. Bij 7/45 had de cardioloog een psychiatrische diagnose ('hyperventilatie') gesteld.

Conclusie: Bij 83% van de patiënten die zich op de Maastrichtse EHH meldden met cardiale klachten, maar zonder cardiale oorzaak en met een HADS-score ≥ 8, werd paniekstoornis en/of depressie vastgesteld.

INLEIDING

Patiënten op de polikliniek Cardiologie of op de Eerste Harthulp (EHH) hebben geregeld klachten van pijn op de borst of hartkloppingen. Bij de helft van de poliklinieкpopulatie en ongeveer eenderde deel van patiënten op de (EHH) met dit soort klachten kan na analyse geen cardiale genese worden geconstateerd. In een aanzienlijk deel van de gevallen berusten de klachten op een paniekstoornis [1-7]. Miskenning van deze aandoening is groot en patiënten met een paniekstoornis hebben in ongeveer 30% van de gevallen ook een depressie [1, 8]. Pijn op de borst gaat samen met hoge medische consumptie: patiënten bezoeken vaak de huisarts of meerdere specialisten [9-11]. Elders in dit nummer gaan wij in op deze problematiek [12].

In dit artikel worden data gepresenteerd uit een pilotonderzoek over vóórkomen van paniekstoornissen alsmede depressie bij patiënten die zich melden met pijn op de borst of palpitatieklachten, zonder cardiale verklaring voor hun klachten, in een Nederlandse EHH-setting.

PATIËNTEN EN METHODE

In de periode 1 november 1998–31 januari 1999 werden alle patiënten die zich op de EHH van het Academisch Ziekenhuis Maastricht meldden en vervolgens na uitgebreid onderzoek of behandeling naar huis werden ontslagen, psychiatrisch gescreend. Dit gebeurde door middel van een envelop met uitgebreide schriftelijke informatie over het onderzoek, een 'informed consent'-formulier, een retourenvelop en de 'Hospital Anxiety and Depression Scale' (HADS). Bij patiënten die door welke oorzaak dan ook geen envelop hadden meegekregen, werd deze per post nagestuurd. De HADS is een algemeen geaccepteerde lijst om in een ziekenhuispopulatie angststoornissen en depressieve stoornissen te detecteren [13, 14]. De patiënt kon dit formulier en de vragenlijst thuis invullen en terugsturen. Op deze manier kregen wij een overzicht van het vóórkomen van stemmingsproblemen bij EHH-bezoekers.

Cardiologische screening

De cardiologische screening op de EHH bestond minimaal uit anamnese, lichamelijk onderzoek en ECG. Gedurende het verblijf op de EHH vond er telemetrische ritmeregistratie plaats. Vaak werd er ook laboratoriumonderzoek verricht. Bij onzekerheid over de diagnose werd er regelmatig een ergometrie voor ontslag van de EHH verricht, om zodoende tot een juiste diagnose te komen. Bij afwezigheid van een cardiale genese werd vaak besloten tot 'geen cardiologische afwijking' of 'atypische thoracale pijnklachten', conclusies gebaseerd op hetgeen bij een goede cardiologisch-klinische praktijkvoering gebruikelijk is ('good clinical practice').

Gestructureerd interview

Als patiënten met als aanmeldklacht pijn op de borst, hartkloppingen, overslagen of pijn in de linker arm, de keel, de schouderbladen of in epigastrio, waarvoor de cardioloog geen cardiale verklaring kon geven, op de HADS een score ≥ 8 hadden, werden zij uitgenodigd voor een interview op de polikliniek cardiopsychiatrie. De grenswaarde van 8 op de HADS was arbitrair, echter, in de literatuur wordt dit als een reële afkapwaarde gehanteerd voor een algemene ziekenhuispopulatie [13, 14].

Door middel van een gestructureerd interview, de 'Mini international neuropsychiatric interview (MINI)[15], afgenomen door steeds dezelfde onderzoekers (een cardioloog en/of een psychiater), werd beoordeeld of er een paniekstoornis was of depressie volgens DSM-IV-criteria. De MINI is een betrouwbaar en gevalideerd meetinstrument ten opzicht van de 'Composite international diagnostic interview' en de 'Structured clinical interview for DSM IIIR patients' [16]. De onderzoekers waren getraind in het afnemen van een MINI. In de meeste gevallen waren zij niet geblindeerd voor de cardiologische EHH-diagnose.

RESULTATEN

Patiënten

In een periode van 3 maanden bezochten 1236 patiënten de EHH van het Academisch Ziekenhuis Maastricht. Van hen werden 621 na uitgebreid onderzoek of behandeling weer ontslagen; zij vormden de screeningspopulatie. Van deze 621 patiënten werd bijna 10% (60 patiënten) geëxcludeerd vanwege onder andere dementie, overlijden, taalproblemen of woonplaats meer dan 50 km buiten de regio.

Van de overgebleven 561 patiënten (gemiddelde leeftijd 60,9 jaar (SD: 13,8); uitersten: 19-91;

309 (55%) mannen en 252 (45%) vrouwen) meldden 401 patiënten (71%) zich met pijn op de borst, hartkloppingen, overslagen of pijn in de linker arm, de keel, de schouderbladen of in epigastrio. Van de patiënten hadden er 160 (29%) andere klachten. Van deze 401 patiënten hadden er 251 (63%) geen cardiale diagnose; 134 (53%) van deze 251 patiënten gaven informed consent, 18 (7%) gaven aan niet mee te willen doen, en 99 (40%) reageerden niet. De resterende 134 patiënten vormden de onderzoekspopulatie (figuur 1).

De gemiddelde leeftijd van deze onderzoekspopulatie was 55,9 jaar (SD: 13,2; uitersten: 23-84). Het betrof 72 (54%) mannen en 62 (46%) vrouwen; 49 (36%) van hen hadden geen cardiale voorgeschiedenis, 67 (50%) wel en 18 (13%) waren voorheen cardiologisch onderzocht zonder dat er afwijkingen waren gevonden. De verwijzer was bij 53 (40%) de huisarts, 71 (53%) bezochten op eigen initiatief de EHH, de overige 10 (7%) kwamen via de Gemeentelijke Geneeskundige Dienst, een polikliniek Cardiologie of een andere polikliniek of de ECG-dienst.

Uitvallers

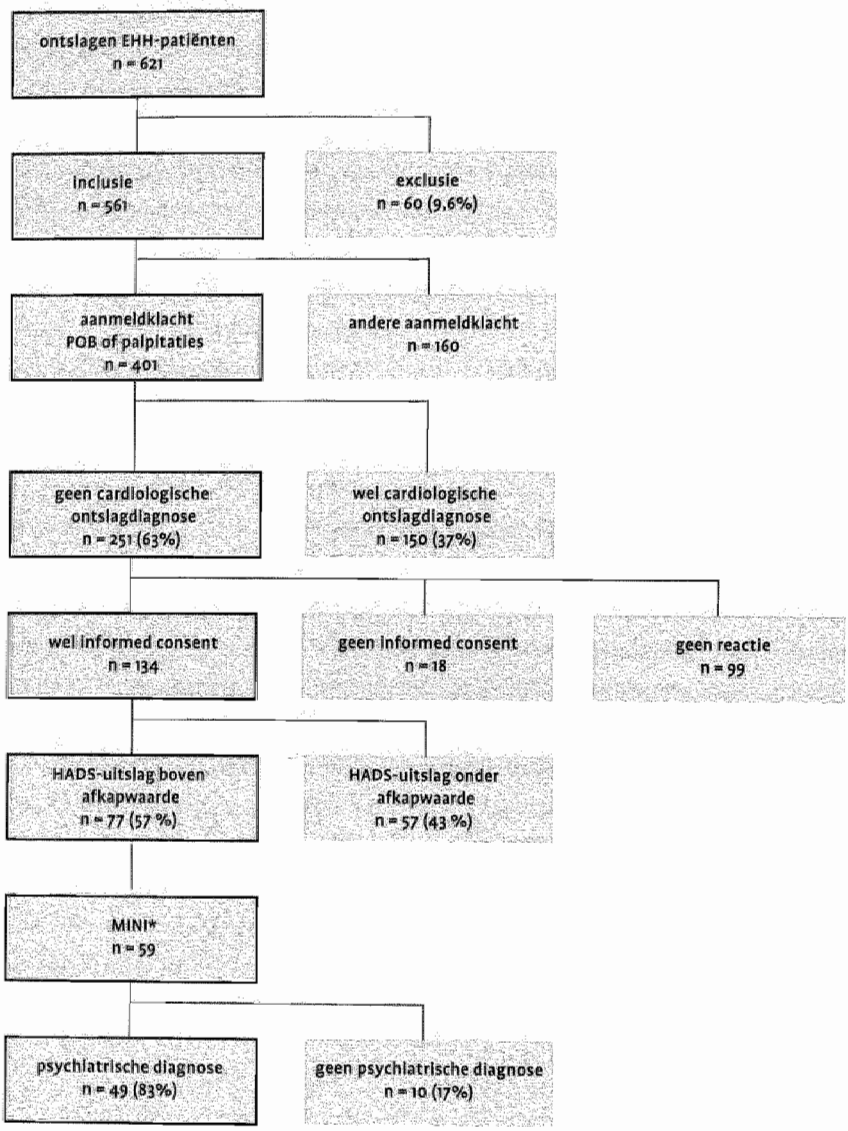
De groep van 117 patiënten die niet meededen, bestond uit 99 patiënten die niet reageerden en 18 patiënten die aangaven niet mee te willen doen (zie figuur 1). De groep die niet reageerde, verschilde met betrekking tot voorgeschiedenis, leeftijd en geslacht niet significant van de groep die wel informed consent gaf. Wel was er een significant verschil wat betreft de verwijzer: in 78% van de gevallen was de huisarts de verwijzer en 17% kwam zelf, ten opzichte van 40% huisarts en 53% zelf ($p = 0,02$).

De groep die bewust niet meedeed (weigeraars; n=18), verschilde significant van de groep die informed consent gaf met betrekking tot cardiologische voorgeschiedenis, geslacht en verwijzer; de leeftijd was niet significant verschillend. Van de weigeraars hadden er 5 (25%) een cardiale voorgeschiedenis versus 67 (50%) in de informed-consentgroep ($p = 0,02$). De weigeraars waren 14 (78%) vrouwen versus 62 (45%) in de informed-consentgroep ($p = 0,01$). Tenslotte was de verwijzer de huisarts bij respectievelijk 14 (78%) en 53 (40%) en kwamen respectievelijk 3 (17%) en 71 (53%) ($p = 0,05$) patiënten uit zichzelf.

HADS en MINI

Van de 134 patiënten scoorden 77 (57%) boven het afbreekpunt van de HADS. Van hen weigerden 3 een gestructureerd diagnostisch gesprek, 15 anderen waren niet meer te traceren of kwamen ondanks herhaalde uitnodigingen hun afspraak niet na. Deze groep was wat betreft leeftijd, geslacht en cardiale voorgeschiedenis niet significant afwijkend van de groep bij wie wel een MINI werd afgenomen. Derhalve bleven er 59 van de 77 potentiële

FIGUUR 1 | **Stroomdiagram van de patiëntengroepen in een pilotonderzoek naar paniekstoornissen op de Eerste Harthulp (EHH) van het Academisch Ziekenhuis Maastricht**



POB = pijn op de borst;
HADS = 'Hospital anxiety and depression scale';
MINI = 'Mini international neuropsychiatric interview';
* de overigen waren weigeraars of verschenen niet op de afspraak.

kandidaten over voor een MINI. Het MINI-responspercentage was daardoor 77. Het betrof 30 mannen en 29 vrouwen; 33 hadden een cardiale voorgeschiedenis, 21 hadden geen cardiale voorgeschiedenis en 5 waren in het verleden cardiologisch onderzocht zonder dat er afwijkingen waren gevonden. Dit onderscheid werd gemaakt om vast te stellen dat zowel patiënten met als zonder cardiologisch verleden een paniekstoornis kunnen krijgen.

Psychiatrische diagnosen

Bij 49/59 patiënten (83%; 95%-betrouwbaarheidsinterval: 73-91) werd met behulp van de MINI een psychiatrische diagnose gesteld ('paniekstoornis' en/of 'depressie'). Bij 21 (43%) was er een paniekstoornis en bij 28 (57%) een depressieve stoornis (zie figuur 1). Bij 24 patiënten (49%) was er comorbiditeit van paniekstoornis en depressie. Bij 24 (53%) patiënten met een paniekstoornis ging deze gepaard met agorafobie. De gemiddelde totale HADS-scores van de 49 patiënten met een psychiatrische diagnose waren als volgt: wel paniekstoornis, geen depressie: 19,4; geen paniekstoornis, geen depressie: 15,5; wel paniekstoornis, wel depressie: 27,3; geen paniekstoornis, wel depressie: 23,2. Bij 7/45 patiënten (13%) met een paniekstoornis werd door de cardioloog hyperventilatie gediagnosticeerd, waarbij wij veronderstellen dat de diagnose 'hyperventilatie' vergelijkbaar is met 'paniekstoornis'. Bij 5 van de 7 patiënten bij wie de cardioloog deze diagnose stelde, was er tevens comorbide depressie.

Het percentage psychiatrische diagnosen was gelijkelijk verdeeld over de 3 groepen 'wel cardiale voorgeschiedenis', 'geen cardiale voorgeschiedenis' en 'cardiologisch onderzocht, maar geen afwijkingen gevonden'. De cijfers waren respectievelijk 28/33 (84%), 17/21 (80%) en 4/5 (80%).

BESCHOUWING

In ons pilotonderzoek van 3 maanden richtten wij ons vooral op het onderzoeken van het vóórkomen van paniekstoornis en/of depressie bij patiënten die zich melden met klachten van pijn op de borst, hartkloppingen, overslagen of pijn in de linker arm, de keel, de schouderbladen of in epigastrio op een Nederlandse EHH, waarbij de cardioloog geen cardiale genese voor de klachten kon constateren. Bij 83% van deze patiënten werd een van deze psychiatrische diagnosen gesteld.

Van alle patiënten gaf 53% toestemming voor deelname, 7% gaf aan niet mee te willen doen. Een beperking van dit pilotonderzoek is uiteraard het ontbreken van psychiatri-

sche gegevens van de overige 40% van de patiënten. Van de patiënten die wel meededen en de HADS terugstuurden, scoorde de helft boven de vooraf gestelde afkapwaarde van 8. Deze hoge waarde maakte de kans gering op fout-negatieve uitslagen. In de literatuur is de gemiddelde sensitiviteit en specificiteit van de HADS in een ziekenhuispopulatie voor het ontdekken van depressie of angst 0,8 of hoger [14].

In onze populatie was de gemiddelde leeftijd 55,9 jaar (SD: 13,2; uitersten: 23-84). Het betrof 54% mannen en 46% vrouwen. Bij een paniekpopulatie in een niet EHH-setting is de gemiddelde leeftijd meestal lager, en ook is het percentage vrouwen meestal hoger [12].

Door het beperkte aantal patiënten bij wie er uiteindelijk een psychiatrisch interview (MINI) werd verricht (n=59; 24% van de 251 die zich aanmeldden met pijn op de borst, hartkloppingen, overslagen of pijn in de linker arm, de keel, de schouderbladen of in epigastrio bij wie geen cardiologische diagnose kon worden gesteld), zou in ons pilotonderzoek selectiebias aanwezig kunnen zijn. De gevonden percentages dienen daarom met enige voorzichtigheid geïnterpreteerd te worden met betrekking tot de totale groep van EHH-bezoekers. Bij screening van HADS-negatieve patiënten zou het gevonden percentage van 83% met een psychiatrische diagnose bijvoorbeeld mogelijk hoger zijn geweest. Feit blijft dat het vóórkomen van paniekstoornis of depressie in deze specifieke groep patiënten hoog is. Een andere beperking is dat wij patiënten die zich meldden met dyspnoe of duizeligheid, symptomen die ook zouden kunnen passen bij paniekstoornis, niet in het onderzoek betrokken. Dit betrof 62 patiënten. De gevonden comorbiditeit van paniekstoornis met depressie van 41% komt overeen met literatuurdata [12].

De gevonden significante verschillen tussen de groep weigeraars en de groep die niet reageerde op de vraag om mee te doen met het onderzoek, stemmen overeen met literatuurdata. In de literatuur zijn er conflicterende resultaten gevonden wat betreft leeftijd van non-respondenten: in onze populatie was dit verschil evenmin significant. Ook wat betreft het geslacht zijn er conflicterende data: diverse onderzoeken vonden dat er meer mannen non-respondenten waren, een aantal onderzoeken vond geen verschil. Onlangs is er door onze onderzoeksgroep bij hartinfarctpatiënten gevonden dat het met name significant meer vrouwen zijn ($p = 0{,}0006$) die weigeren om mee te doen (niet gepubliceerde resultaten).

In ons onderzoek was de herkenning van patiënten met een paniekstoornis door de cardioloog, op grond van de veronderstelling dat de diagnose 'hyperventilatie' gelijk is aan paniekstoornis, 13%. Dit percentage is hoger dan de 2% dat in de literatuur wordt gemeld [1]. Oorzaak hiervan zou kunnen zijn dat door het onderzoek de aandacht voor paniekstoornis in de differentiaaldiagnose groter was, waardoor deze eerder werd onderkend.

De klinische betekenis van de gevonden resultaten is, dat er bij een aanzienlijk deel van de patiënten die bij de cardioloog onder behandeling komen en bij wie deze geen cardiale afwijking vindt ondanks een duidelijk herkenbaar cardiaal klachtenpatroon, sprake is van een psychiatrische stoornis. Bij een aanzienlijk deel van de patiënten met pijn op de borst of palpitaties ligt paniekstoornis ten grondslag aan de gepresenteerde klachten, bij een ander deel kan het een comorbide probleem zijn naast het cardiologisch lijden. Echter, in beide gevallen dient dit adequaat behandeld te worden. Het behoort ook tot de taken van de cardioloog om paniekstoornis hoog in de differentiaaldiagnose te houden en hierop te screenen en de patiënt, indien nodig, door te verwijzen naar de desbetreffende specialist.

CONCLUSIE

Ook in een Nederlandse setting is paniekstoornis of depressie een frequent voorkomend probleem bij patiënten die zich op een EHH melden met klachten van pijn op de borst of hartkloppingen en bij wie geen cardiale oorzaak wordt geconstateerd. Bij 83% van de patiënten uit de geselecteerde onderzoekspopulatie kon na een gestructureerd psychiatrisch interview een psychiatrische diagnose worden gesteld ('paniekstoornis' en/of 'depressie'). De herkenning van deze aandoeningen door cardiologen was laag. Bij patiënten bij wie behoudens de paniekstoornis ook een depressie aan de orde was, leek herkenning door de cardioloog beter te zijn. De bruikbaarheid van de HADS als screeningsinstrument in de EHH-setting voor het herkennen van patiënten met een mogelijke paniekstoornis wordt momenteel in een groter onderzoek in het Academisch Ziekenhuis Maastricht vastgesteld.

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4

4 |

Effect of treatment of panic disorder in patients with frequent ICD discharges: a pilot study

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ABSTRACT

Anxiety and depression are common in patients receiving an implantable cardioverter defibrillator (ICD). An association between the number of ICD discharges and mood disturbances has been found. We performed a pilot study in ICD patients with frequent ICD shocks having a comorbid diagnosis of panic disorder with agoraphobia and depression, in which we treated them with a combination of a selective serotonin reuptake inhibitor (SSRI) and a behavior program. We hypothesized that this intervention would result in a decrease of ventricular premature beats or arrhythmias and possibly in a reduction of number of shocks. Four of five patients treated with such a combination therapy experienced no discharge of the ICD during a 6 month follow-up. The total number of ventricular premature beats decreased significantly after treatment. There was also clear psychiatric improvement. These results warrant larger scale studies on the pathophysiological mechanisms as well as treatment issues.

INTRODUCTION

Background

The implantable cardioverter defibrillator (ICD) is an effective and life saving therapy for potentially lethal ventricular arrhythmias [1] and its use is rapidly increasing worldwide. However, ICD discharges may be accompanied by or result in psychosocial and psychiatric sequelae.

It is not clear from literature what the prevalence of psychiatric disorders before ICD implantation is. Some studies found no premorbid psychiatric predisposition before implantation [2,3], where other studies excluded those with premorbid psychiatric problems [3,4]. Depression ranges from 6.5% up to 58% [5–12] in patients after ICD implantation. For panic disorder (PD) or agoraphobia, numbers range from 5%–19.4% [4,5,12], whereas other studies show that some form of anxiety is present in 24%–87.5% of ICD patients [2–5,12].

ICD implantation itself may decrease anxiety significantly [10]. ICD discharge, however, increases anxiety and decreases confidence, leading to panic disorder through classic conditioning [2– 4,10,11]. Herrmann [5] found that with increasing numbers of ICD shocks, the percentage of psychologically distressed ICD patients rose.

Several studies found that anxiety and depressive symptoms before and after ICD implantation are significant independent predictors of arrhythmias and frequent shocks [4,6,8,13]. Clearly, based on literature, it can be stated that a substantial degree of anxiety or depressive symptoms are present in ICD patients, that the presence of anxiety symptoms is related to rhythm disturbances and that ICD discharges may trigger the occurrence of depressive symptoms, PD and avoidance behavior.

Based on the possible relationship between affective dysregulation and arrhythmias, a pilot study was performed in order to investigate whether treatment of PD, agoraphobia and depressive symptoms with a combination of a selective serotonin reuptake inhibitor (SSRI) and a behavior program in ICD patients with frequent ICD shocks could result in a decrease of ventricular premature beats (VPB's) or ventricular arrhythmias and a reduction of number of shocks.

METHODS

Patients with frequent ICD discharges (defined as at least 3 events the last year) and PD were referred to the Med-PsychUnit (MPU) of the University Hospital, Maastricht, The

Netherlands. This is a multi-disciplinary unit, where the departments of Psychiatry, Cardiology, Internal Medicine and Neurology cooperate in the diagnostic work-up and treatment of patients with combined somatic and psychiatric problems. A diagnosis of PD and agoraphobia and depressive symptoms was made using the Mini International Neuropsychiatric Interview (MINI) [14,15].

The 14 items Hospital Anxiety and Depression Scale (HADS) [16] was obtained on admission and after 1 and 3 weeks of hospital stay. The HADS was repeated at 1 and 3 months after discharge from the MPU. There was a 6 months follow-up period, consisting of 3 months psychiatric follow-up and 6 months follow-up for ICD related events.

At baseline, during hospitalization, and the two follow-up visits (at 1 and 3 months), 24h holter registrations were performed to measure VPB's or ventricular arrhythmias. VPB's were expressed as the total number of VPB's per 24h, as well as percentage of the total number of QRS-complexes per 24h during the holter registration. As far as the 6 months ICD related events is concerned, events were defined as a defibrillation shock, cardioversion (CV), or antitachycardia pacing (ATP). ATP is a rapid, low energy ICD pacing signal given in case of tachyarrhythmia; CV shock is a high energy shock given in case of ventricular fibrilation or ventricular tachycardia which was not stopped by ATP.

All patients were treated with paroxetine starting with 20 mg daily. If necessary, the paroxetine dose was adjusted during hospitalization. Paroxetine was chosen because of its proven efficacy in treatment of PD and depression and local experience with this drug. There was no pharmaceutical sponsoring of this pilot study. The patients were concurrently involved in a behavior program to counteract avoidance behavior. The behavioral treatment program consisted of education on the nature of panic attacks, how to cope with them and counteracting avoidance behavior with gradual exposure. It was also explained to the patient that in the beginning of the treatment with paroxetine, panic attacks could become initially more frequent.

During the study all patients were kept on the same cardiac medication.

RESULTS

Five ICD patients with PD, agoraphobia, and depression (2 women and 3 men) were admitted to the MPU. Age range was 61–74, mean 67.4 ± 5.1 years. Time since ICD implantation ranged between 3.5–57 months, mean 28.7 ± 23.4 months. Three patients experienced a resuscitation before ICD implantation. Three patients had documented coronary artery

TABLE 1 | **Clinical characteristics and baseline data of the 5 ICD patients**

Case number	1	2	3	4	5
Age	74	66	65	71	61
Sex	F	F	M	M	M
Months ICD	3.5	50	57	18	15
Betabl	yes	yes	yes	yes	yes
LVEF %	64	42	25	25	55
ATP	0	2	17	266	134
Shocks	3	6	6	34	6

Months ICD = months since implantation ICD; betabl = beta blocking agent;
LVEF = left ventricular ejection fraction; ATP = antitachy pacing; F = female; M = male.

TABLE 2 | **Follow-up data of HADS, holter registration and ICD events at 1 (FU1), 3 (FU2), and 6 months**

Case	Baseline			3 weeks		
	24h VPB %	HADS anx	HADS dep	24h VPB %	HADS anx	HADS dep
1	0.22	18	10	0.06	—	—
2	10.28	15	12	4.03	15	13
3	3.11	17	12	0.37	10	11
4	0.07	15	15	0.30	6	3
5	1.64	15	18	0.81	3	4
mean	3.064	16	13.4	1.114	8.5	7.7

Case	Follow-up 1			Follow-up 2			6 months	
	24h VPB %	HADS anx	HADS dep	24h VPB %	HADS anx	HADS dep	ATP FU	Shocks FU
1	0.01	4	2	0.031	4	2	0	0
2	2.83	10	14	—	8	9	0	0
3	0.23	5	2	1.60	8	2	58	27
4	0.06	3	3	0.089	6	7	0	0
5	0.51	3	8	3.44	5	8	0	0
mean	0.726	5.0	5.8	1.137	6.2	5.6		

HADS anx = score HADS anxiety subscale; HADS dep = score HADS depression subscale; 24h VPB% = 24h holter registration, number VPB's expressed as percentage of total QRS complexes; ATP = antitachycardia pacing; CV = cardioversion; Def = defibrillation; — = data not available.

disease of which 2 had a previous myocardial infarction. One patient had a dilated cardiomyopathy. One patient had on echocardiography a posterior wall infarction but normal coronary arteries on coronary angiography. The LVEF ranged from 25%–64%, mean 42.2% ± 17.5%. As far as previous psychiatric history is concerned, 4 of 5 patients had experienced some psychiatric complaints before ICD implantation. Two patients had been previously treated because of depressive and anxiety complaints.

Baseline HADS anxiety score ranged from 15–18, mean 16 ± 1.4. Baseline HADS depression score ranged from 10–18, mean 13.4 ± 3.1. Baseline total HADS score ranged from 27–33, mean 29.4 ± 2.3. The mean number of VPB's per 24h as percentage of the total QRS complexes was 3.82% ± 4.50 on baseline. The mean absolute number of VPB's per 24h was 2,278.4 ± 2,797. The mean number of ATP the year before treatment was 83.8. The mean number of CV the year before treatment was 10.2. The mean number of defibrillations the year before treatment was 0.8.

Mean duration of MPU admission was 3.8 weeks. See also table 1 for baseline characteristics.

During admission, complaints and avoidance behavior decreased in most patients. Two patients needed a reduction of their Ace-inhibitors because of hypotension, probably due to inhibition of the CP450 enzyme system by paroxetine. At the end of hospitalization the mean dose paroxetine prescribed was 40 mg. This dose was unchanged during follow up. Psychiatric symptoms decreased as measured by questionnaires (table 2) as did agoraphobic behavior. In sum, in all variables listed in table 2, a clinically significant effect could be observed.

The mean number of VPB's per 24h as percentage of the total QRS complexes decreased from 3.82% ± 4.50 before treatment to 1.34% ± 1.68 after treatment (FU1) ($P = .04$). The mean absolute number of VPB's per 24h decreased from a mean of 2,278.4 ± 2,797 (baseline) to 535.8 ± 899.9 (follow up 1). This is a reduction of 77%. The mean number of ATP the year before treatment was 83.8 and decreased to 11.6 on the 6 month follow up. The mean number of CV the year before treatment was 10.2, after the 6 months follow up period 5.4. The mean number of defibrillations the year before treatment was 0.8, after 6 months follow up 0 (table 2).

During 6 months cardiological follow up, no ICD discharges, CV or ATP occurred in 4 patients (table 2). One patient (Case 3) was admitted 4 months after his hospital stay with frequent shocks and ATP due to ventricular tachycardia. These events appeared to be related to progressive worsening of his left ventricular function. However, it has to be emphasized that 4 patients had no ICD events after treatment.

DISCUSSION

In this pilot study of 5 ICD patients with frequent discharges of their ICD, diagnosed with PD, agoraphobia, and a depressed mood, treatment of their psychiatric condition, using paroxetine and a behavior program, resulted in clinical improvement both from a psychiatric as well as a cardiological perspective. After a follow-up period of 6 months, 4 of the 5 patients experienced no discharges of their ICD. In all patients the total number of VPB's decreased significantly after treatment. Our findings should be interpreted with caution because of the small sample size. However, it seems very likely that the cardiac improvement is associated with the psychiatric treatment, because the patients became "electrically more stable", as documented by holter registrations, which showed a decrease of premature ventricular beats during and after treatment despite the fact that no cardiac medication was changed in this time period.

The exact mechanism is as yet not clear. There might be a direct effect of paroxetine on electrophysiological level of the heart, or via improvement of behavioral factors that in turn can influence several biological pathways such as heart rate variability (HRV) or HPA-axis. It is known that in depression HRV is decreased, but can be restored by treating depression [17]. We did not measure HRV or cortisol or other biological substances, so no definite answer can be given. The fact that in several patients a reduction of the ACE-inhibition was needed after start of the paroxetine because of hypotension could, apart from inhibition of the CP450 system, be influenced by the fact that the patients might be less compliant with their ACE-inhibition intake before admission.

Whether anxiety or depression are the trigger(s) for arrhythmias or shocks or frequent arrhythmias or shocks are the trigger for developing psychopathology is not clear. In literature, there is evidence for both hypotheses. Only prospective studies in ICD patients with extensive psychiatric baseline measurements and a combined psychiatric and cardiological follow up, can shed more light on these questions. While the underlying mechanism of improvement is as yet unclear, we believe that the high incidence of PD with agoraphobia and/or depression in patients with an ICD justifies a randomized controlled trial of our approach in a larger group of patients.

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PART B | *diagnostic issues*

5

5 |

Validity of the Hospital Anxiety and Depression Scale (HADS) for use with patients with non cardiac chest pain

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ABSTRACT

Consecutive patients seen in the first-heart-aid service of a university hospital and given a diagnosis of non cardiac chest pain completed the self-report Hospital Anxiety and Depression Scale (HADS). Patients with a score ≥ 8 on either the anxiety or depression subscale (N=266, mean age=55.81 years, SD=13.03, 143 male patients) were compared with patients scoring < 8 (N=78, mean age=60.55 years, SD=10.84, 50 male patients) by means of the Mini International Neuropsychiatric Interview. Panic disorder and/or depression identified by the diagnostic interview were highly prevalent in the group with a score ≥ 8 (73.3% versus 3.9% in the comparison group). The HADS is an adequate screening instrument for the detection of affective disorders in patients with non cardiac chest pain.

INTRODUCTION

Panic disorder with or without comorbid depression is common among patients presenting to a first-heart-aid setting [1], yet it often remains unrecognized as a cause of chest pain or palpitations [2]. In a pilot study in a first-heart-aid service of a hospital, a diagnosis of panic disorder and/or depression was received by 83% of patients presenting with non cardiac chest pain or palpitations who scored above 8 on either the anxiety or depression subscale of the Hospital Anxiety and Depression Scale (HADS). In only 15% of this group was a possible psychiatric problem recognized by the treating cardiologist [2].

Patients with non cardiac chest pain or palpitations impose a large burden on the health care system. They have a high level of health care consumption, including frequent hospital admissions, numerous outpatient or first-aid visits, and repeated diagnostic investigations that may present a risk for iatrogenic complications [1].

The negative influence of anxiety as well as depression on cardiac prognosis both in patients after myocardial infarction as well as in healthy subjects has been clearly established [1,3,4]. The quality of life of non cardiac chest pain patients with panic disorder is markedly poor [5].

These findings suggest the need for a simple and validated screening instrument for use in the hospital first-heart-aid service to identify patients who have panic disorder and/or depression underlying non cardiac chest pain.

The HADS [6] is a reliable and valid instrument for assessing anxiety and depression in medical patients [7,8]. It includes an anxiety subscale and a depression subscale, each of which contain seven questions. Validation studies for the HADS have been performed in various somatically compromised populations [9-11]. Herrmann et al. [12] suggested that the HADS may be considered the standard instrument for assessing anxiety and depression in cardiac patients.

Although the HADS is frequently used in research, it has not been validated for use with patients presenting with non cardiac chest pain or palpitations. In this study, the sensitivity and specificity of the HADS for use in assessing such patients was evaluated by using the Mini International Neuropsychiatric Interview as the gold standard [13].

METHOD

Subjects

The study participants were patients who presented to the first-heart-aid service of the University Hospital Maastricht between January 2000 and February 2002. They presented with chest pain, pain in their left arm or shoulder or epigastric region, or palpitations. Cardiological screening consisted of a full medical history, physical examination, and ECG. Additional tests, such as laboratory measurements of cardiac enzymes and troponin, exercise testing, echocardiography, or chest X-ray, were performed as needed, according to standard cardiological practice.

Procedure

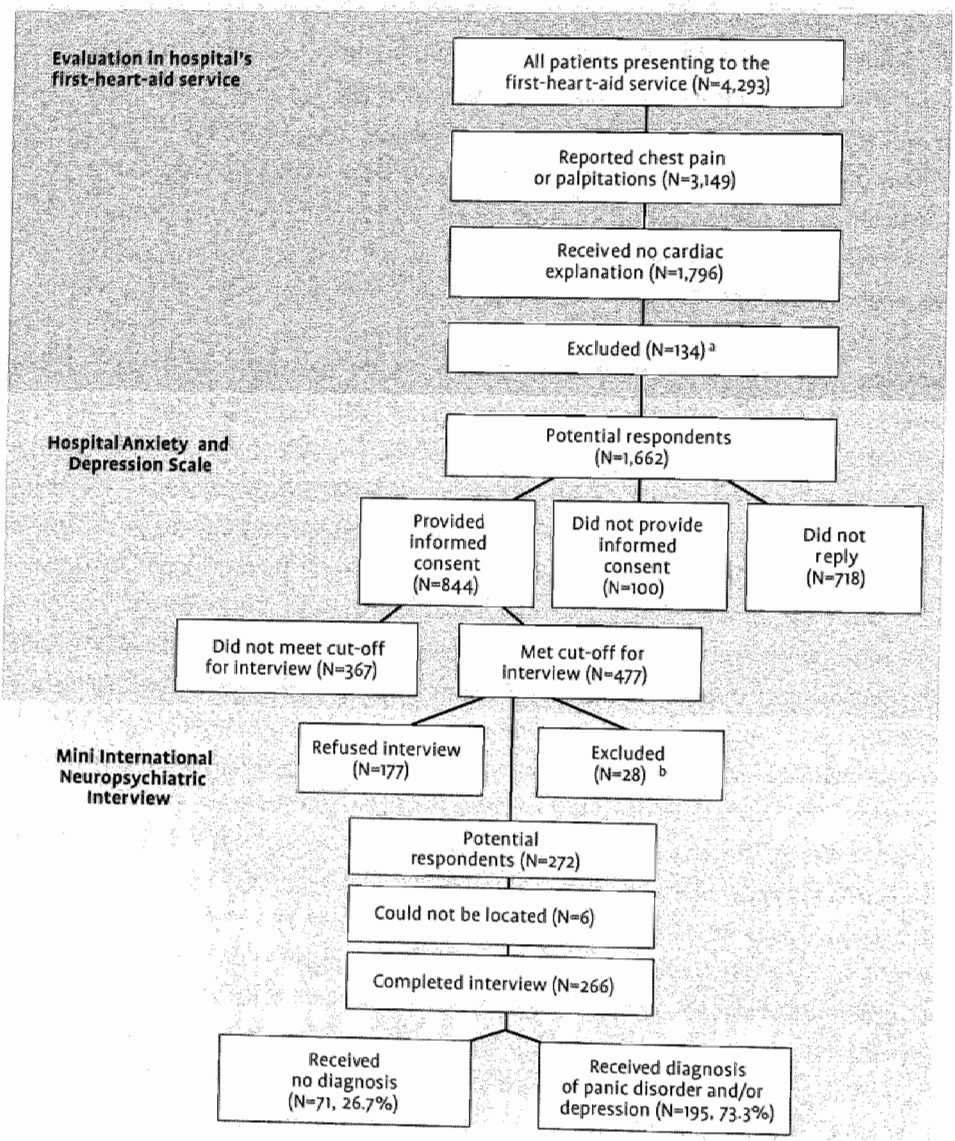
Patients who had been discharged from the hospital's first-heart-aid service with a diagnosis of atypical chest pain, non cardiac origin of the complaints, no cardiac abnormalities, non cardiac chest pain, or hyperventilation received an envelope by mail. This envelope contained information about the study, an informed consent form, the HADS, and an envelope in which to return the completed scale and consent form. Patients who did not return the HADS within 2 weeks received a reminder phone call.

Patients with dementia, those who lived more than 50 km from the hospital, and those who did not speak Dutch were excluded. Patients who returned the HADS and had a score ≥ 8 on either the anxiety or depression subscale were invited back to the hospital to be interviewed with the Mini International Neuropsychiatric Interview, which is based on the DSM-IV criteria. The cut-off value of 8 was determined on the basis of a review of previously published studies [7]. The interviews were performed by a cardiologist (P.K.) and a psychiatrist or psychiatric resident who had been trained in using the Mini International Neuropsychiatric Interview. The interviewers were not blind to the cardiological diagnosis received by the patient in the hospital's first-heart-aid service. A comparison group consisting of consecutive patients who had been evaluated in the first-heart-aid service and had been discharged with no cardiac diagnosis but who scored below the cut-off score of 8 on either the anxiety or the depression subscale of the HADS were also interviewed with the Mini International Neuropsychiatric Interview. The study was approved by the local ethical committee.

Statistics

To determine the optimal cut-off scores, receiver operating characteristics curves [14] were obtained for the HADS. The receiver operating characteristics curve plots sensitivity and

FIGURE 1 | **Subjects in phases of the study on the validity of the HADS in screening patients with non cardiac chest pain presenting to a hospital's first-heart-aid service**



[a] Excluded were patients with dementia, those who lived ≥50 km from the hospital, and those who did not speak Dutch.
[b] Excluded were patients found to have a cardiological cause for their initial complaint.

'1–specificity' (1 minus specificity) for every possible cut-off score. The optimal cut-off score is determined visually by assessing which score combines maximal sensitivity with maximal specificity. The scale with the largest area under the curve is better for distinguishing between depressed and non-depressed patients or between patients with and without anxiety disorders. In addition, positive predictive values and negative predictive values were measured for different cut-off scores in the central range of the scale scores.

All analyses were performed with Statistical Package for Social Sciences (SPSS) release 10. Differences between groups were analysed by using t tests and chi-square tests. The results were considered statistically significant if $p<0.05$.

RESULTS

Characteristics of the Study Patients

Between January 2000 and February 2002, 4,293 patients visited the first-heart-aid service of the University Hospital Maastricht. Of those patients, a total of 3,149 (73%) had chest pain, pain in their left arm or shoulder or epigastric region, or palpitations. Of this group, 1,796 (57%) received no cardiac explanation for their complaints (received a diagnosis of atypical thoracic complaints or hyperventilation). Of those patients, 134 were excluded for reasons such as dementia, living more than 50 km from the hospital, or not speaking the Dutch language. Of the remaining 1,662 patients, 844 (50.8%) returned the HADS by mail. One hundred patients (6.0%) refused to participate. Patients with a HADS score ≥ 8 on either subscale were invited to complete the Mini International Neuropsychiatric Interview. Four hundred seventy-two patients (56.5%) scored above the cut-off value. One hundred seventy-seven patients (37.1%) refused the structured interview. Twenty-eight patients of the remaining 300 were excluded because they were found to have what appeared to be a cardiological cause of the initial complaint. Six patients could not be traced or did not come for the interview, despite repeated efforts by the researchers to locate them. The remaining 266 patients were interviewed with the Mini International Neuropsychiatric Interview (figure 1).

The comparison group, composed of patients who did not score above the cut-off score of 8 on the HADS, consisted of 78 patients. The baseline characteristics of both groups are reported in table 1.

The two groups differed significantly in age but did not differ in gender, previous cardiac history, and complaints when presenting to the first-heart-aid service. As table 1 shows,

TABEL 1 | **Baseline characteristics of patients with non cardiac chest pain presenting to a hospital's first-heart-aid service who scored above and below the cut-off value on the HADS**

Characteristic	Above the cut-off value (N=266)[a]		Below the cut-off value (N=78)[b]		Analysis
	Mean	SD	Mean	SD	p (t test)
Age					
Years	55.81	13.03	60.55	10.84	0.001
	N	%	N	%	p (chi-square test)
Gender					
Male	143	53.8	50	64.1	n.s. (0.11)
Female	123	46.2	28	35.9	
Previous cardiac history					
No	100	37.6	20	25.6	n.s. (0.06)
Yes	104	39.1	41	52.6	
Screened, no abnormalities	31	11.7	5	6.4	
Unknown	31	11.7	12	15.4	
Complaint					
Chest pain or pain in the arm, shoulder, or epigastric region	245	92.1	76	97.4	n.s. (0.10)
Palpitations	21	7.9	2	2.6	
Diagnosis					
Atypical thoracic complaints	233	87.6	75	96.2	0.03
Hyperventilation	33	12.4	3	3.8	
	Mean	SD	Mean	SD	p (t test)
HADS scores					
Depression subscale	9.24	4.33	1.85	2.47	<0.001
Anxiety subscale	12.03	3.54	3.27	2.67	<0.001
	N	%	N	%	p (chi-square test)
MINI diagnosis					
No diagnosis	71	26.7	75	96.1	0.04
Panic disorder	80	30.1	0	0.0	
Depression	13	4.9	2	2.6	
Panic disorder and depression	102	38.3	0		
Other diagnosis	0	0.0	1[c]	1.3	

[a] Score ≥ 8 on either the anxiety or depression subscale of the Hospital Anxiety and Depression Scale.

[b] Score < 8 on either the anxiety or depression subscale of the Hospital Anxiety and Depression Scale.

[c] Dysthymia.

the patients who scored below the cut-off score on the HADS were more likely to have received a diagnosis of atypical thoracic complaints and less likely to have received a diagnosis of hyperventilation, compared with the patients who scored above the cut-off. (We collected data on the frequency of a diagnosis of hyperventilation because this diagnosis probably reflects some recognition by the cardiologist of a psychiatric or psychological problem in the patient.)

Of the patients who scored above the cut-off value on either the anxiety or the depression subscale of the HADS, 95.1% scored above the cut-off on the anxiety subscale, compared with 2.6% of the patients who scored below the cut-off score on either subscale ($p<0.001$). Of the patients who scored above the cut-off on either subscale, 63.2% scored above the cut-off score on the depression subscale, compared with 3.8% of the patients who scored below the cut-off score on either subscale ($p<0.001$).

Affective Disorders

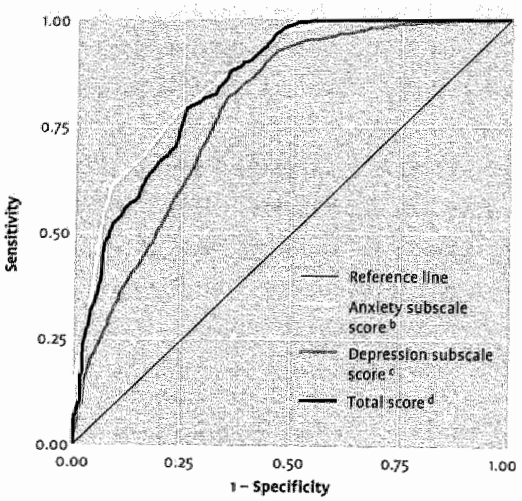
Among the patients who scored above the cut-off value on either subscale of the HADS, 38.3% received a diagnosis of panic disorder combined with a depressive episode on the basis of the Mini International Neuropsychiatric Interview, compared with none of the patients who scored below the cut-off value on either subscale. Thirty percent of the patients who scored above the cut-off value on either subscale received a diagnosis of panic disorder, compared with none of the patients who scored below the cut-off value. Of the patients who scored above the cut-off value on either subscale, 4.9% received a diagnosis of a depressive disorder, compared with 2.6% of the patients who scored below the cut-off value. No psychiatric diagnosis was identified on the basis of the Mini International Neuropsychiatric Interview in 26.7% of the patients who scored above the cut-off value on either subscale and in 96.1% of the patients who scored below the cut-off value. Patients who scored above the cut-off value on either subscale were significantly more likely to receive a diagnosis of panic disorder and/or depression than the patients who scored below the cut-off value ($p=0.04$).

Cut-off values

The optimum cut-off scores on the HADS for detecting panic disorder and/or depressive episode according to the Mini International Neuropsychiatric Interview are shown on the receiver operating characteristics curve (figure 2).

For the HADS anxiety subscale, the optimum cut-off score for screening purposes was 8/9, with a sensitivity of 88% and a specificity of 64%. For diagnostic purposes a high

FIGURE 2 | **Receiver operating characteristics curve for the HADS in a study of patients with non cardiac chest pain presenting to a hospital's first-heart-aid service[a].**



[a] Receiver operating characteristics of the Hospital Anxiety and Depression Scale assessed with reference to the Mini International Neuropsychiatric Interview.
[b] Area under the curve = 0.90.
[c] Area under the curve = 0.85.
[d] Area under the curve = 0.90.

TABLE 2 | **Presence of a diagnosis of panic disorder and/or depression in patients with non cardiac chest pain presenting to a hospital's first-heart-aid service who scored above and below the cut-off value on the HADS[a].**

	Patients who scored above the cut-off value (N=266)[c]		Patients who scored below the cut-off value (N=78)[d]	
Diagnosis of Panic Disorder and/or Depression[b]	N	%	N	%
Yes (N=198)	195	73.3	3	3.8
No (N=146)	71	26.7	75	96.2

[a] Sensitivity 98.48%; specificity 51.36%; positive predictive value 73.30%; negative predictive value 96.15%.
[b] Based on the Mini International Neuropsychiatric Interview.
[c] Score ≥ 8 on either the anxiety or depression subscale of the Hospital Anxiety and Depression Scale.
[d] Score < 8 on either the anxiety or depression subscale of the Hospital Anxiety and Depression Scale.

specificity is important. For diagnostic purposes, the optimal cut-off score on the anxiety subscale was 10/11, with a specificity of 84% and a sensitivity of 69%. On the receiver operating characteristics curve, the area under the curve was 0.90 for the anxiety subscale.

For the HADS depression subscale, the optimum cut-off score for screening purposes was 4/5, with a sensitivity of 88% and a specificity of 57%. For diagnostic purposes the optimal cut-off score on the depression subscale was 3/4, with a specificity of 92% and a sensitivity of 54%. The area under the curve for the depression subscale was 0.85.

For the total score on the HADS, the optimum cut-off score for screening purposes was 11/12, with a sensitivity of 97% and a specificity of 54%. For diagnostic purposes, the optimal cut-off score on the HADS depression subscale was 18/19 with a specificity of 83% and a sensitivity of 64%. The area under the curve for the total score was 0.90.

DISCUSSION

In their updated literature review on the validity of the HADS as a screening instrument, Bjelland et al. [8] suggested that a cut-off score of 8 for both the anxiety and depression subscales most frequently results in an optimal balance between sensitivity and specificity of approximately 80%. This threshold was found in the general population as well as in somatically compromised populations. We found other cut-off values in the specific group of patients in our study, suggesting that the validity of self-report questionnaires cannot be generalized over populations with different somatic conditions.

Our results suggest that the optimal cut-off score on the HADS anxiety subscale for screening for panic disorder and/or depressive episode in atypical chest pain patients is 8/9. The optimal cut-off score on the depression subscale for screening for depressive episode and/or panic disorder is 4/5. For the total score, the optimal cut-off value for screening for depressive episode and/or panic disorder is 11/12.

The comparison patients, who scored below the cut-off value on the HADS, were as a group significantly older than the patients who scored above the cut-off score (p=0.001) (table 1). This finding suggests that psychiatric diagnoses such as panic disorder and depression may be more prevalent in younger patients with atypical chest pain [1].

Compared with patients who scored above the cut-off value, comparison patients were more likely to have a previous cardiac history (52.6% versus 39.1%) (p=0.06). Patients with a previous cardiac history who experienced atypical chest pain might have been more easily reassured by the cardiologist at the first-heart-aid service and thus might have re-

ported fewer complaints of anxiety or depression on the HADS.

A limitation of the study was the high number of patients who refused to participate in the study, which could mean that the patients who were willing to participate could constitute a biased group. In addition, the participating patients may have completed the HADS at home with the help of a spouse, family member, or partner, which could have influenced the results.

Despite these limitations, the study results suggest that the HADS is a sensitive screening instrument for patients with non cardiac chest pain or palpitations who are frequent utilizers of the cardiac health care system. The HADS can be used as a practical screening instrument in a first-heart-aid service setting. Patients who score above the cut-off score should be referred to a psychiatry outpatient clinic for further diagnosis and treatment. Such intervention could help prevent a long-term pattern of poor quality of life, frequent utilization of first-aid or outpatient clinics, and worse cardiovascular prognosis, even in the absence of known cardiac disease.

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6 |

Non cardiac chest pain in the Emergency Department:
the role of cardiac history and Type D personality

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submitted

ABSTRACT

Background

Non cardiac chest pain (NCCP) is common in patients presenting to Emergency Departments (ED) and is frequently associated with panic disorder (PD), representing a major burden for patients and the health care system. Little is known about patient characteristics that increase the risk of NCCP. We examined whether cardiac history or Type D personality were associated with PD and/or depression driven NCCP.

Methods and results

Patients presenting with NCCP to the ED of the University Hospital Maastricht were screened using the Hospital Anxiety and Depression Scale (HADS). Patients scoring ≥ 8 on either HADS subscale were invited for a psychiatric interview; a consecutive sample of patients scoring < 8 on the HADS was included as a reference group. Type D personal-

ity (tendency to experience emotional distress) was assessed with the DS14. Among the 304 HADS-positive patients, 89% were diagnosed with PD/depression as compared to 8% of the 106 HADS-negative patients. Previous cardiac history was not associated with psychiatric diagnosis. Type D patients reported more anxiety symptoms (12,4±4,0 vs. 8,1±4,9) and depression symptoms on the HADS (10,2±4,7 vs. 5,8±4,9) and more often had comorbid PD/depression (91/157=58% vs. 57/253=23%) than non-Type D patients ($p<0.0001$). Type D personality (OR=8.67, 95%CI 4.69-16.02), younger age and male sex were independently associated with increased risk of PD or depression. Type D was independently associated with comorbid PD/depression (OR=14.49).

Conclusion

Type D personality, but not cardiac history, is independently associated with the presence of psychopathology in NCCP. Type D is associated with a substantially increased risk of co-occurring PD/depression in these patients.

INTRODUCTION

Each year, more than 6 million patients in the United States present to Emergency Departments (ED) with chest pain or other symptoms suggestive of myocardial ischemia [1]. A large part of this group is hospitalized, but cardiac etiology is found in less than one-third of this group [1]. In the light of risk stratification and health care costs containment, the effectiveness of chest pain centres within ED's has been subject of recent research [1]. Chest pain or palpitations of non cardiac origin are common in patients presenting to ED's and outpatient clinics. Half of the patients in a multidisciplinary chest pain unit without coronary artery disease (CAD) had active gastroesophageal or anxiety disorders [1].

Panic disorder (PD) is an anxiety disorder often found in patients presenting with chest pain; prevalence of PD in an ED setting ranges between 16% and 75% with a mean of 31% [2]. Chest pain frequently occurs during a panic attack [1, 3], but PD often remains unrecognized because patients themselves may primarily report somatic symptoms (chest discomfort) rather than psychological symptoms (fear) [2]. PD has important consequences for the health care system, including risk of frequent hospital admissions, unnecessary diagnostic investigations and iatrogenic complications [4]. In addition, quality of life is markedly decreased in chest pain patients with PD [5]. Hence, the clinical care or work up of patients presenting with chest pain may benefit from routine psychological screening [6].

The co-occurrence of PD and depression is high. Approximately 50-60% of patients with a major depression report a lifetime history of anxiety disorders such as PD [7].

In addition, anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients [8, 9]. The 'distressed' or Type D personality has also been related to morbidity and long-term mortality risk in patients with coronary heart disease [10, 11]. Type D personality refers to the combination of the tendency to experience negative emotions and the tendency to inhibit self-expression in social interaction.

Little is known, however, about depression, PD and Type D personality in patients with non cardiac chest pain. We therefore examined (i) the role of depression and the co-occurrence of PD in patients with non cardiac chest pain and (ii) the role of cardiac history versus Type D personality in PD and depression in these patients.

To answer these questions we performed an observational study in a large cohort of patients presenting with non cardiac chest pain to a First-Heart-Aid (FHA) and who underwent a standardised psychiatric assessment to diagnose PD and depression.

METHODS

Patients

The study population consisted of patients presenting to the FHA of the University Hospital Maastricht (May 2000-December 2002). This is an annex to the ED specifically dedicated to patients presenting with cardiac complaints. Details of the screening methods have been published elsewhere [12].

Cardiological screening consisted of a full history, physical examination and 12-lead electrocardiogram (ECG). Additional tests such as laboratory measurements of cardiac enzymes and troponin, exercise testing, echocardiography, chest X-ray or other diagnostic investigations thought necessary were performed according to good clinical cardiological practice. Following these tests, patients with chest pain of at that moment non cardiac origin were approached for inclusion in the study. Patients who suffered from dementia, living more than 50 kilometres from the hospital or not speaking the Dutch language were excluded. All participating patients signed an informed consent form. The Hospital Ethics Committee approved the study.

Screening for anxiety and depression

Patients discharged from the First-Heart-Aid with a diagnosis of chest pain or palpita-

tions of non cardiac origin received an envelope by mail. This envelope contained information on the study, an informed consent form, the Hospital Anxiety and Depression Scale (HADS) and a return envelope for the HADS. The HADS is a self-report questionnaire consisting of 14 questions, divided into an anxiety subscale (7 questions) and a depression subscale (7 questions). It is a reliable and valid instrument for assessing anxiety and depression in medical patients [13, 14] and in patients presenting with non cardiac chest pain [12, 14]. If patients did not return the HADS within 2 weeks, they received a reminder phone call. Patients scoring on either HADS subscale ≥ 8 were invited for a psychiatric diagnostic interview. A consecutive cohort of non cardiac chest pain patients scoring < 8 on both HADS subscales was also included in the study to comprise a reference group of patients with low levels of anxiety and/or depression. The cut-off point of 8 on the HADS scale was based on literature [12].

Psychiatric diagnosis of anxiety and depression

The Mini International Neuropsychiatric Interview (MINI) was used as structured diagnostic psychiatric interview to diagnose PD and depression [15, 16]. The MINI diagnosis of psychiatric disorders is based on Diagnostic and Statistical Manual (DSM) IV criteria. A cardiologist (PK), psychiatrist (AH), or resident in psychiatry performed the interviews. All interviewers were trained in performing the MINI. They were not blinded for the cardiological diagnosis made at the FHA.

Type D personality

Type D personality, i.e. the combination of the tendency to experience negative emotions and the tendency to inhibit self-expression, was assessed using the Type D Scale-14 or DS14 [11]. The DS14 comprises a 7-item subscale measuring negative affectivity (the first personality component of Type D) and a 7-item subscale measuring social inhibition (the second personality component of Type D). Cronbachs' α of these subscales is good, namely 0.88 and 0.86, respectively. These subscales are also stable over time, as indicated by 3-month test-retest correlations $r = 0.72$ and 0.82, respectively, and are not dependent on changes in mood and health status [11]. A cut-off of 10 on both DS14 subscales was used to classify patients as Type D, resulting in 157 Type D patients and 253 non-Type D patients with non cardiac chest pain.

Statistical Analyses

Analyses were done with Statistical Package for Social Sciences release 11 for Apple Macin-

tosh. Differences between groups were analysed using independent sample t-tests. Data are presented as mean ± standard deviation. Cross tabulation was used to examine the association between Type D personality and psychiatric diagnosis. Logistic regression analysis was used to evaluate the independent predictors of psychopathology. All tests were two-tailed.

RESULTS

In the period May 2000-December 2002, we analysed 410 NCCP patients: 304 HADS positive patients and 106 HADS negative patients. Baseline characteristics are found in table 1. As far as cardiac history is concerned: 42% of the Type D population had a previous cardiac history compared to 50% of the non Type D population (p=ns). Mean age in the HADS group scoring high on affective symptoms was lower as compared to the group scoring low on affective symptoms (p=0.023). There were slightly more males in the HADS negative group (p=ns). Compared to a 'normal' psychiatric PD population (patients presenting with anxiety to a psychiatric or psychological setting), our population (presenting with somatic symptoms) was older and included more male patients [17].

Co-occurrence of depression and PD in the HADS positive group

Only 10% of the patients in the HADS positive group (n= 304) had no psychiatric diagnosis. The majority of HADS positive patients had a comorbid psychiatric disorder: 48,7% (n=148) of this group had a current depressive episode as well as PD (figure 1). In 41,1% (n=125) of the patients, there was also agoraphobia diagnosed. Only 5,3% (n=16) had a single diagnosis of depression, whereas 34,5% had PD (n=105).

Within the group of patients having comorbid depression and panic (n=148), there were 52% males and 48% females (mean age 55,16 ± 13,01 years). Within the group with a single psychiatric diagnosis (n=156) there were 59% males and 41% females (mean age 57,44 ± 12,99 years). There were no statistically significant differences between the double psychiatric diagnosis group and the single psychiatric diagnosis group with reference to age, previous cardiac history and gender.

When comparing the depression and PD group with the single psychiatric diagnosis group, it appeared that the mean HADS anxiety score was 12,99 ±3,75 versus 11,18 ± 3,15. Accordingly, the mean HADS depression score was 11,23 ± 4,02 and 8,01 ± 4,14, respectively (all p values < 0.0001).

TABLE 1 | Baseline data of the HADS positive and HADS negative group

	HADS positive N=304	HADS negative N=106	p-value
Age	56.33 ± 13.03 (21-85)	59.66 ± 12.72 (24-83)	0.023
Sex			ns*
Male	56%(169)	62% (66)	
Previous cardiac history			ns*
Yes	45% (137)	52%(55)	
Previous psychiatric history			< 0.0001
Yes	47 % (143)	19% (20)	
Current psychiatric diagnosis			
PD†	35% (105)	6% (6)	
Depression	5% (16)	2% (2)	
Depression and PD†	49% (148)	0%	< 0.0001
No diagnosis	10% (31)	90% (95)	
Other diagnosis	1% (4)	3% (3)	
Type D personality			< 0.0001
Yes	49% (150)	7% (7)	
HADS ‡ anxiety score	12.06 ± 3.57	3.11 ± 1.76	< 0.0001
HADS ‡ depression score	9.58 ± 4.38	1.55 ± 1.86	< 0.0001

*ns= not significant †PD= Panic Disorder ‡HADS= Hospital Anxiety and Depression Scale
Age and HADS scores are presented as mean ± SD (range). Other data are presented as % and (N).

The role of Type D personality

The diagnosis of Type D personality was not significantly associated with age, sex and previous cardiac history (table 2). Only 7 patients from the HADS negative group were diagnosed as Type D personality. The prevalence of Type D in the HADS positive group was 49,3% versus 6,6% in the HADS negative group (p= <0.0001).

Fourteen patients (8,9%) of the Type D group had no psychiatric diagnosis according to the MINI psychiatric interview, whereas 90% of the Type D patients were diagnosed with PD and/or depression. In the Type D group, 58% had a double psychiatric diagnosis versus 23% in the non-Type D group (table 2). Stratifying patients by history of cardiac disease indicated that Type D personality was significantly associated with double psychiatric diagnosis in both patients with and without history of cardiac disease (figure 2).

TABLE 2 | **Characteristics of the Type D and non Type D patients**

	Type D N=157	Non Type D N=253	p-value
Age	56.71 ±12.99	57.49 ± 13.05	ns*
Sex			
Male	58% (91)	57% (144)	ns*
Previous cardiac history			
Yes	42% (66)	50% (126)	ns*
Previous psychiatric history			
Yes	52% (82)	35% (88)	< 0.0001
Current psychiatric diagnosis			
PD†	26% (41)	28% (70)	
Depression	6% (9)	4% (9)	
Depression and PD†	58% (91)	23% (57)	< 0.0001
No diagnosis	9% (14)	44% (112)	
Other diagnosis	1% (2)	2% (5)	
HADS ‡ anxiety score	12.44 ± 4.02	8.08 ±4.93	< 0.0001
HADS ‡ depression score	10.19 ± 4.70	5.83 ± 4.86	< 0.0001

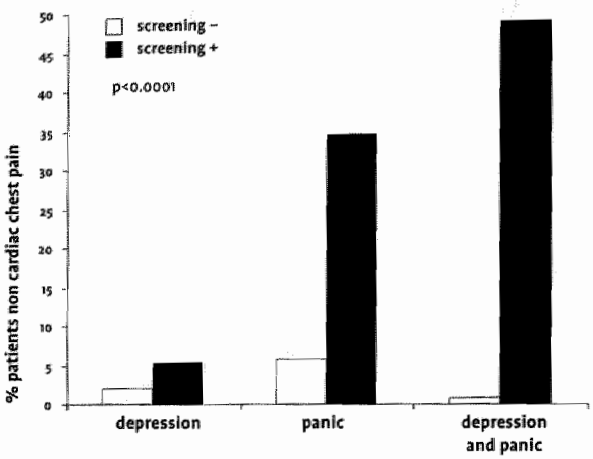
*ns= not significant †PD= Panic Disorder ‡HADS= Hospital Anxiety and Depression Scale
Age and HADS scores are presented as mean ± SD (range). Other data are presented as % and (N).

TABLE 3 | **Type D personality as independent predictor of psychopathology**

Variable	Odds ratio (95% CI)	p-value
Single psychiatric diagnosis		
Age	0.97 (0.95 – 0.98)	<0.0001
Male sex	1.62 (1.01 – 2.61)	0.046
History of cardiac disease	1.23 (0.89 – 1.71)	0.21
Type D Personality	8.67 (4.69 – 16.02)	< 0.0001
Double psychiatric diagnosis		
Age	0.96 (0.94 – 0.98)	0.001
Male sex	2.20 (1.21 – 3.97)	0.009
History of cardiac disease	1.17 (0.83 – 1.64)	0.37
Type D Personality	14.49 (7.35 – 28.5)	< 0.0001

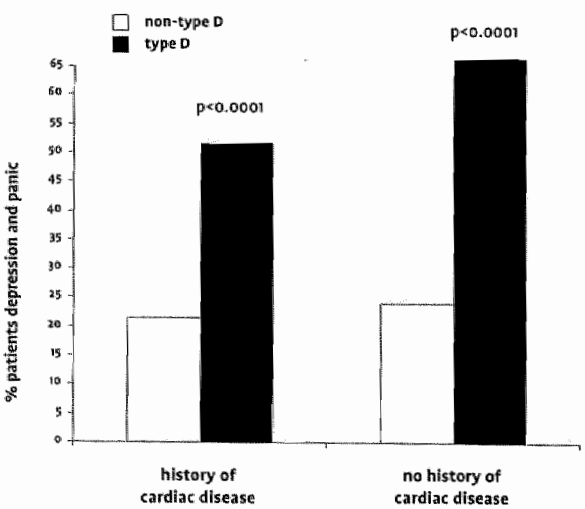
Single psychiatric diagnosis: depression or panic disorder
Double psychiatric diagnosis: depression and panic disorder

FIGURE 1 | Percentage of patients who were diagnosed with depression, panic or depression and panic, stratified by screening for psychological symptoms



Screening + = presence of psychological symptoms as indicated by HADS score ≥ 8 on either subscale
HADS = Hospital Anxiety and Depression Scale
Psychiatric diagnosis was made using a structured psychiatric interview (MINI) [18]

FIGURE 2 | Percentage of patients with combined depression and panic, stratified by cardiac history and Type D personality



Psychiatric diagnosis was made using a structured psychiatric interview (MINI) [18]

Independent predictors of psychopathology

To examine whether Type D was an independent risk factor for having a diagnosis of depression and/or PD in patients with non cardiac chest pain, we performed a logistic regression analysis for the total group of 410 patients. This regression model included age, gender and previous cardiac history.

Using single psychiatric diagnosis (depression or PD) as an endpoint, Type D personality (OR 8.67, 95%CI 4.69-16.02), age (OR 0.97, 95% CI 0.95-0.98) and male sex (OR 1.62, CI 1.01-2.61) were retained as independent predictors independently associated with psychopathology, but not previous cardiac history (table 3, top). Type D personality (OR 14.49, 95% CI 7.35-28.5), age (OR 0.96, 95% CI 0.94-0.98) and male sex (OR 2.20, 95% CI 1.21-3.97) were also independently associated with the double psychiatric diagnosis of depression and PD (table 3, bottom). History of cardiac disease was not associated with psychiatric diagnosis.

DISCUSSION

In the present study, the prevalence of psychopathology (PD and/or depression) in patients presenting with NCCP and/or palpitations to a chest pain clinic and scoring high on affective symptoms, was very high. Especially the double psychiatric diagnosis of both PD and depression was common among patients reporting symptoms of distress. It is well known that this leads to high medical utilization and medical costs [18]. In recent years, studies have been performed in chest pain centres to improve risk stratification in chest pain patients [1, 2, 19-29]. This has lead to the notion that screening of chest pain patients can still be optimised, in order to improve the quality of care and lower health care costs.

In previous research, we showed that the HADS is an adequate screening instrument to evaluate patients with non cardiac chest pain for anxiety or depressive symptoms, in order to perform an adequate referral to psychiatric specialist help [12]. Until now, personality characteristics such as Type D have not been studied in NCCP patients, however. Type D personality is related to increased morbidity and mortality in cardiac patients [30], even after invasive treatment with a drug-eluting stent [31]. Type D has also been associated with increased levels of anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator [32].

The findings from the present study suggest that the psychological screening of NCCP patients may also be optimalised by including the Type D scale. There was a high prevalence of Type D personality in the HADS positive group compared to the HADS negative

group (49,3% vs. 6,6%, p<0.0001). Of note, this personality diagnosis was not the result of a cardiac history; i.e., Type D personality was equally prevalent among patients with and without a previous cardiac history. Type D personality was associated with an eight-fold increased risk of psychopathology, controlling for previous cardiac history, age and sex. In addition, Type D personality was independently associated with co-occurring PD and depressive disorder. Finally, 52% of the NCCP patients with Type D personality had a previous psychiatric history compared to 35% of the non-Type D patients (p<0.0001). This finding supports the notion that Type D personality is a vulnerability factor for chronic emotional and social difficulties that are relatively stable across time and situations.

This study has a number of limitations. First, its cross-sectional design does not allow for the determination of cause and effect. Hence, it is not clear whether Type D personality leads to PD/depression or vice versa, although evidence from prospective research indicates that Type D personality is an independent predictor of emotional distress in CAD patients [30]. Secondly, our sample consisted of relatively more male and older patients than is typically observed in PD populations [7]. It is also unclear why psychopathological disorder was more prevalent among male patients as compared to female patients; this finding in NCCP patients is at variance with research in psychiatric patients. Therefore, the present findings may not be generalized to other patient populations. This study was performed from a clinical point of view. One can never be 100% sure that the chest pain is 'non cardiac', but cardiological clinical routine according to good clinical practice ruled out that there was a cardiac cause of the complaints at that specific moment.

This study also has a number of strengths. The number of patients included in the study is higher compared to other studies on PD, and we included a reference group of patients suffering from NCCP but without psychiatric disorder. PD and depression were not inferred from patients' self-reports but were diagnosed following a structured interview [15, 16] according to objective psychiatric criteria. This is also the first study to look carefully at the co-occurrence of anxiety (PD) and depression. Finally, this is the first study to demonstrate that Type D personality may be of value not only in CAD but also in NCCP. Type D personality has never before been used in a sample of patients presenting with chest pain.

The finding goes well beyond the confirmatory nature of the observation that NCCP often has psychiatric components, rather suggesting that screening for Type D personality would help to identify patients at risk for persistent chest pain complaints. Preliminary evidence suggests that personality disorder may be associated with poor outcome of psychiatric treatment in patients with NCCP and PD [33, 34], but more research is needed to

examine whether personality traits may predispose to PD [35]. The present findings suggest that this may actually be the case in non cardiac chest pain, and warrant further prospective research on Type D personality and vulnerability to chronic psychopathological disorder in these patients.

As noted earlier, NCCP may increase the risk of unnecessary health care utilization and iatrogenic complications [4] as well as impaired quality of life [5]. Although chest pain complaints frequently occur during a panic attack [1, 3], psychological risk factors often remains unrecognized because patients themselves may primarily present somatic rather than psychological symptoms [2]. Hence, the clinical care of patients presenting with chest pain may benefit from routine psychological screening [6], including screening for Type D personality traits.

CONCLUSION

Psychiatric pathology, especially panic disorder and depression, is common in patients presenting with NCCP. Type D personality is frequently present in patients with PD and/or depression driven chest pain and/or palpitations. Type D personality was associated with an eight-fold increased risk of psychiatric pathology and a fourteen-fold increased risk of psychiatric co-morbidity, independent from all other risk factors. Younger age and male sex were also associated with an increased risk for psychopathology and psychiatric co-morbidity. Previous cardiac history was not associated with psychopathology.

As panic disorder and depression are important for cardiac prognosis, general well being and health care costs, chest pain clinics should screen for anxiety and depressive symptoms in patients presenting with NCCP, in order to treat these conditions. Future prospective studies are needed to study the effect of Type D personality on psychiatric as well as cardiac prognosis in non cardiac chest pain and its treatment. We are currently conducting an intervention study with a selective serotonin reuptake inhibitor in this specific population. This study may help to elucidate the effect of Type D personality on psychiatric as well as cardiac outcome.

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Diagnosing panic disorder as cause of non cardiac chest pain: *value of the 35% CO_2 challenge test*

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ABSTRACT

Objective: Chest pain and/or palpitations of non cardiac origin are common in Emergency Department (ED) and chest pain clinic populations and often due to panic disorder (PD) and/or depression. These patients have a high health care consumption, chronic course of symptoms and deterioration of cardiac prognosis. This stresses the need for a validated diagnostic instrument to identify PD in patients presenting with non cardiac chest pain or palpitations.

Methods and results: We studied the CO_2 challenge test as a diagnostic instrument in 30 patients with non cardiac chest pain scoring ≥ 8 on both anxiety or depression subscale of the 14-items Hospital Anxiety and Depression Scale (HADS) and subsequently diagnosed with PD and/or depression, and in 24 patients scoring < 8 without a psychiatric diagnosis. The specificity of the CO_2 challenge test was 87.5% and the sensitivity 63.3%. The positive

predictive value was 79.2% and the negative predictive value was 66.3%. There were no clinically relevant and electrocardiographic significant changes during CO_2 challenge.
Conclusion: The CO_2 challenge test triggers non cardiac chest pain specifically in patients presenting with non cardiac chest pain and diagnosed with PD and/or depression. The test is safe and easy to administer and should follow the HADS screening.

INTRODUCTION

Each year more than 6 million patients in the United States present to Emergency Departments (ED's) with chest pain or other symptoms suggestive of myocardial ischemia [1]. A large part of this group is hospitalized, but cardiac etiology is found in less than one-third [2]. The effectiveness of chest pain centers as far as risk stratification and health care costs is concerned, has been subject of recent research [2, 3]. Chest pain or palpitations of non cardiac origin are common in patients presenting to ED's and outpatient clinics. Half of the patients in a multidisciplinary chest pain unit without coronary artery disease (CAD) had active gastro-esophageal or anxiety disorders [4]. Panic disorder (PD) is an anxiety disorder often found in patients presenting with chest pain; prevalence of PD in an ED setting ranges between 16% and 75% with a mean of 31% [5]. Although chest pain often occurs during a panic attack [4, 6], PD often remains unrecognized because patients themselves may primarily report somatic symptoms (chest discomfort) rather than psychological symptoms (fear) [5].

PD is a chronic condition with important consequences for the health care system, including risk of frequent hospital admissions, unnecessary diagnostic investigations and iatrogenic complications [7]. In addition, quality of life is markedly decreased in chest pain patients with PD [8]. Also, anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients [9, 10], but also in patients with anxiety without a previous cardiovascular history [11, 12].

The co-occurrence of PD and depression is high. Approximately 50-60% of patients with a major depression report a lifetime history of anxiety disorders such as PD [13].

Hence, there is an emerging need for changes in the care of patients presenting with atypical chest pain possibly suffering from PD [14]. This stresses the importance of effective screening for psychopathology in this large group of patients, requiring a validated instrument to identify PD in patients presenting to an ED or chest pain center with chest pain or palpitations [5].

METHODS

The object of our pilot study was to investigate the value of the CO_2 challenge test as a diagnostic instrument in a PD and/or depression driven non cardiac chest pain population. This study was part of a larger study.

Patients

The study population consisted of 2 consecutive cohorts of patients presenting to the First Heart Aid (FHA) of the University Hospital Maastricht. This is an annex to the ED and specifically dedicated to patients presenting with cardiac complaints. For organizational reasons the data collection was done in 2 periods: June 2000-December 2000 and February 2001-July 2001. In these 2 periods, patients scoring ≥ 8 as well as < 8 on either anxiety or depression subscale of the HADS (the HADS positive and HADS negative group resp.) were studied. A detailed description of the methods used is stated elsewhere [15].

The cardiologist or resident in cardiology screened all patients presented at the FHA. This work-up consisted of a full history, physical examination and 12-lead ECG. Generally additional tests such as laboratory measurements of cardiac enzymes (ASAT, ALAT, CK) and troponin or other laboratory measurement such as hemoglobin or infection parameters were carried out. Often exercise testing, echocardiography, chest X-ray or other diagnostic investigations thought necessary were performed according to good clinical cardiological practice. During their stay on the FHA the patients' heart rhythm was continuously monitored. Following these examinations patients diagnosed with non cardiac chest pain were approached for the study, irrespective of a previous cardiac history.

As there was no literature available on the safety of a CO_2 challenge test for patients with an extensive previous cardiac history, we excluded patients for this pilot study who had suffered from a previous MI or were known with proven severe CAD. Patients suffering from pulmonary disease were also excluded.

Screening

Patients discharged from the FHA with a diagnosis of chest pain or palpitations of non cardiac origin received an envelope by mail. This envelope contained information on the study, an informed consent form, the HADS and a return envelope for the HADS. The HADS is a self-questionnaire consisting of 14 questions, divided into an anxiety subscale (7 questions) and a depression subscale (7 questions). It is an adequate and validated screening instrument for the detection of affective disorders in patients with non cardiac chest pain

(NCCP), with a sensitivity of 98.5% and a specificity of 51.4% [15]. If patients did not return the HADS within 2 weeks they received a reminder phone call.

If patients returned the HADS and the score on either subscale was ≥ 8, they were invited for a standardized diagnostic psychiatric interview (Mini International Neuropsychiatric Interview, MINI) according to the Diagnostic and Statistical Manual IIIR [16]. Parallel to this patient group, the HADS negative control group consisted of a consecutive cohort of patients in the same period, who followed the same FHA procedure, were discharged with no cardiac diagnosis and scored < 8 on either HADS subscale. A MINI was also performed in all these HADS negative patients.

The cut-off point of 8 on the HADS scale was based on literature [15]. The cardiologist (PK) and a psychiatrist (AH) or resident in psychiatry performed the interviews. The interviewers were trained in performing the MINI. They were not blinded for the cardiac diagnosis made at the FHA, nor for the score on the HADS. Patients known with dementia, living more than 50 kilometers from the hospital or not able to speak the Dutch language were excluded.

All participating patients signed informed consent forms. The local ethical committee approved the study.

CO_2 challenge procedure

Patients were instructed before the procedure, and were told that possibly aroused symptoms would appear shortly after inhalation and disappear just as quickly. Panic attacks were never referred to as such. It was explained that first their vital capacity had to be measured, followed by blood pressure. Patients were given the Visual Analogue Anxiety Scale (VAAS, range 0: no anxiety to 100: worst anxiety imaginable) and the 13 items Panic Symptom List (PSL), consisting of the 13 DSM-III R panic symptoms with scores for each symptom ranging from 0 (not present) to 4 (very severe).

The gas mixture of 35% CO_2 and 65% O_2 was applied and inhaled by the patient taking a deep breath (at least 80% of their initial vital capacity) through a self-administered apparatus followed by breath holding for 4-5 seconds [17]. After this, subjects were allowed to exhale. Immediately thereafter blood pressure was measured again. Before, during and after CO_2 inhalation a 12-lead electrocardiogram (ECG) was recorded. Complaints of chest pain and/or palpitations were recorded and patients were asked whether the complaints after provocation were the same as their usual spontaneous complaints. The inhalation of CO_2 was expressed as a percentage of the initial vital capacity (%CO_2 of vital capacity inhalation). The cardiologist (PK) performed all challenge tests. The percentage CO_2 of vital

TABLE 1 | **Baseline characteristics of patients presenting with chest pain or palpitations of non cardiac origin, scoring above (HADS positive group) and under (HADS negative group) the cut-off score on the HADS**

Variable	HADS positive n=30	HADS negative n=24	p-value
age	53.90 ± 10.44	58.42 ± 8.74	0.10
sex	19 (63.3 %) male	13 (54.2%) male	0.51
Previous cardiac history			
No	12 (40%)	17 (70.8%)	
Yes	5 (16.7%)	2 (8.3%)	0.31
Previous cardiac screening no abnormalities	10 (33.3%)	4 (16.7%)	
Unknown / not stated	3 (10%)	1 (4.2%)	
Mini diagnosis			
Panic disorder (PD)	13 (43.3%)	0	
PD and depression	16 (53.3%)	0	
Depression	1 (3.4%)	0	<0.0001
HADS anxiety score	11.37 ± 3.30	3.42 ± 1.69	<0.001
HADS depression score	7.93 ± 3.71	1.29 ± 0.95	<0.001
Height in cm	171.6 ± 18.1	172.1 ± 9.7	0.84
Weight in kg	78.07 ± 18.08	76.54 ± 13.0	0.73

P-value for comparing the HADS positive group versus the HADS negative group

capacity inhalation could not be determined in 6 patients in the HADS positive group due to technical problems affecting the registration of the inhalation capacity. However, inhalations in these patients were sufficient to include the patient, as the rest of the procedure was carried out properly. The total CO_2 challenge time was about 10 minutes. Normally, in case of a positive response, subjects experience chest pain and/or palpitations starting within ± 30 seconds after inhalation and disappearing after 2-3 minutes. Excessive alcohol consumption and drinks containing xanthine were not allowed 8 hours prior to the test, nor smoking or eating.

Statistics

All analyses were performed with Statistical Package for Social Sciences (SPSS) release 10 for Apple Macintosh. Differences between and within groups were analysed using independent sample T-tests and paired samples T-tests. Because of the small sample size, differences between groups were also calculated using nonparametric testing. This is stat-

ed where applicable. Results of the CO_2 challenge were compared using Chi-square test; p-values ≤ 0.05 were considered as statistically significant.

RESULTS

The HADS positive group consisted of 30 patients, the HADS negative group of 24 patients. Baseline characteristics of both groups are given in table 1.

There were no significant differences (all p values > 0.10) in gender, age, weight and height.

Of the HADS positive group, 73.3% (n=22) had no previous cardiac history. This was the case in 86.7% (n=21) of the HADS negative group (p=0.31). In the HADS positive group, 16,7% (n=5) did have a previous cardiac history. Of these, 2 patients were known with a percutaneous transluminal coronary angioplasty (PTCA), 1 patient had paroxysmal atrial fibrillation and left ventricular hypertrophy, 1 patient had had rhythm surgery for a Wolff Parkinson White syndrome and 1 patient was known with a mitral valve prolapse (MVP).

In the HADS negative group, 8,3% (n=2) had a previous cardiac history; both patients had a MVP. In the HADS positive group, 13 patients were diagnosed with PD only. Sixteen patients suffered from both PD and depression. One patient was diagnosed with a depressive disorder only. In the HADS negative group no psychiatric diagnoses were found after the MINI.

Data concerning the CO_2 challenge are given in table 2. There were no statistically significant differences between both groups as far as heart rate, blood pressure and tidal volume before and after the CO_2 challenge were concerned. The CO_2 challenge resulted in a slight increase in systolic blood pressure and a very minor increase in diastolic blood pressure in both groups (p=ns). Heart rate showed a minor increase in the HADS positive group (p=ns) and a minor decrease in the HADS negative group (p=ns). The percentage of inhaled CO_2 showed no significant differences between both groups.

Symptoms scored on the PSL before the CO_2 challenge were 3.03 ± 3.50 in the HADS positive group and 0.42 ± 0.88 in the HADS negative group (p=0.001). After the challenge, PSL symptoms increased to respectively 14.2 ± 8.1 in the HADS positive group versus 4.8 ± 3.7 in the HADS negative group (p=0.001).

The VAAS score before challenge was 18.2 ± 17.2 in the HADS positive group versus 1.4 ± 2.8 in the HADS negative group (p=0.04). After the challenge, this increased to 42.6 ± 32.5 in the HADS positive group compared to 11.2 ± 15.1 in the HADS negative group (p=0.04).

TABLE 2 | **Results of panic symptoms (PSL), anxiety (VAAS), blood pressure and heart rate before and after the CO_2 challenge test**

Variable	HADS positive n=30			HADS negative n=24			p-value
	pre	post	p np*	pre	post	p npt	np ‡
Heart rate per minute	68.7 ± 11.8	71.8 ± 18.0	ns	70.1 ± 10.9	69.79 ± 11.93	ns	ns
BP syst. in mmHG	129.8 ± 25.3	142.4 ± 29.1	0.002	140.3 ± 19.8	146.0 ± 21.09	0.023	ns
BP diast. in mmHG	83.4 ± 13.2	85.1 ± 13.1	ns	84.0 ± 9.3	85.54 ± 9.34	ns	ns
Tidal volume in liters	3.8 ± 1.1	3.8 ± 1.7 n=24 CO_2	ns	3.64 ± 1.0	3.1 ± 1.4 CO_2	ns	ns
PSL	3.0 ± 3.5	14.2 ± 8.1	<0.001	0.4 ± 0.9	4.8 ± 3.7	<0.001	0.001
VAAS	18.2 ± 17.2	42.6 ± 32.5	<0.001	1.4 ± 2.8	11.2 ± 15.1	0.001	0.04
% CO_2 of vital cap.	101.5 ± 34.2 n=24			87.64 ± 33.86			ns
Result CO_2 test positive Result CO_2 test negative	19 (63.3%) 11 (36.7%)			3 (12.5%) 21 (87.5%)			<0.001

* comparing pre- and post-data of the HADS positive group with each other (non parametric)

† comparing pre- and post-data of the HADS negative group with each other (non parametric)

‡ comparing the HADS positive group with the HADS negative group

Abbreviations: BP: Blood pressure, np: nonparametric, PSL: Panic Symptom List, % CO_2 of vital capacity: inhalation of CO_2 expressed as a percentage of the initial vital capacity, VAAS: Visual Analogue Anxiety Scale

Using validated criteria [18, 19], the CO_2 test showed in 63.3% a positive outcome in the HADS positive group compared to 12.5% positive outcome in the HADS negative group ($p<0.0001$). This resulted in a sensitivity of 63.3% and a specificity of 87.5% with a positive predictive value (PPV) of 79.2% and a negative predictive value (NPV) of 66.3%

Table 3 shows ECG values before and after the CO_2 challenge. There are no significant differences as far as ECG data are concerned between both groups.

There is a small, statistically significant but not clinically relevant change in the electrical axis (from + 24.82 mean to + 29.36 mean, $p=0.01$) as well as in QRS width before and after CO_2 challenge (from 88.12 msec mean to 86.24 msec mean, $p=0.02$). In 5 patients (3 HADS negative and 2 HADS positive patients), a very short lasting sinusbradycardia developed immediately on inhalation, with a minimal heart rate of 51, immediately followed by a sinustachycardia with a maximal heart rate of 90. In 7 patients a decrease in QRS voltage was found in some extremity leads (especially lead 1 and AVL), probably due to increased lung volume following a strong inhalation. This normalized within minutes. Despite the fact that patients experienced chest pain, no ST-T segment changes were seen on the ECG.

DISCUSSION

A CO_2 challenge test can be administered safely to patients presenting to a chest pain center with chest pain or palpitations of non cardiac origin, together with high scores on the HADS and no extensive previous cardiac histories. The test is not accompanied by clinically significant ECG changes, nor changes in heart rate or blood pressure. In our HADS positive group (diagnosed PD and/or depression), 63% had a positive CO_2 challenge test. In psychiatric and physically healthy patients, the CO_2 challenge test is an established diagnostic test for PD [17-19]. Two studies reported on the CO_2 challenge test in patients with PD related chest pain. Beitman et al [20] found that patients with PD and normal coronary arteries were more likely to respond to CO_2 challenge with acute anxiety. Fleet et al [21] investigated 23 patients with CAD and PD and 26 patients with CAD without PD. All PD patients experienced a panic attack, compared to 15% of the control patients [21].

The strength of our study is that we evaluated 2 groups of patients presenting with the same complaints, but one group with and the other group without a psychiatric diagnosis. Limitations of our study are firstly the sample size. Secondly, 53% of the HADS positive group suffered from both PD and depression. As has been shown, co-morbid de-

TABLE 3 | **Electrocardiographic (ECG) data before and after CO_2 challenge**

Variable	HADS positive group n=30			HADS negative group n=24			P-value
	pre	post	p np*	pre	post	p np†	‡
Heart rate bpm	70.4 ± 13.6	72.5 ± 16.8	ns	70.1 ± 11.0	69.8 ± 11.9	ns	ns
PR-interval msec	151.1 ± 20.5	149.1 ± 22.5	ns	151.9 ± 19.7	145.8 ± 16.5	0.004	ns
Frontal QRS axis in degrees	22.0 ± 40.5	28.8 ± 42.9	0.014	25.5 ± 32.5	30.8 ± 28.9	ns	ns
QRS duration msec	88.3 ± 10.7	86.5 ± 9.9	ns	87.5 ± 11.7	85.8 ± 11.3	0.018	ns
QT-interval msec	382.8 ± 33.2	385.2 ± 37.9	ns	382.0 ± 27.5	381.0 ± 34.0	ns	ns
Qtc-interval msec	409.3 ± 11.4	415.2 ± 21.9	ns	407.7 ± 9.2	410.1 ± 12.0	ns	ns

* comparing pre- and post-data of the HADS positive group with each other (non parametric)
† comparing pre- and post-data of the HADS negative group with each other (non parametric)
‡ comparing the HADS positive group with the HADS negative group
np= nonparametric

pression results in a higher sensitivity for CO_2 challenge, which could have influenced the results [22]. Also, our patients were a selected subgroup of motivated patients who filled out the HADS, scored above the cut-off value, had a diagnosis of PD and/or depression on a standardized psychiatric interview, and cooperated in the CO_2 challenge test. Our study group had only minor cardiac abnormalities and no severe cardiac history such as a previous myocardial infarction. Therefore our results can as yet not be generalized for all patients presenting to chest pain centers. However, the CO_2 challenge test can be of important additional help in order to discriminate between cardiac chest pain (which is not provoked by CO_2 challenge) and chest pain as a symptom of a panic attack (which might be provoked by CO_2 challenge). The test does not rule out the presence of CAD, but is indicative of the presence of PD.

Even if patients have normal coronary arteries after coronary angiography, reassurance on the origin of their complaints does not lead to diminished chest pain. Recurrent chest pain will lead to repetitive visits to the ED and even re-catheterization [23]. Therefore, the reproduction of symptoms by performing the CO_2 challenge test is a key element in the screening procedure and a helpful starting point for referring to adequate psychiatric treatment.

Although the sensitivity of the CO_2 challenge seems rather low, it is comparable with the widely used diagnostic exercise test. In general CAD patients, the sensitivity of an exercise test is ± 68% and the specificity ±77%. In patients with one vessel disease, the sensitivity ranges

between ± 25% - 71%, depending on which coronary artery is diseased. Only in patients with multiple vessel disease, the sensitivity increases to ± 81% with a specificity of ± 66% [24].

An additional advantage of provoking panic symptoms by means of a CO_2 challenge test is that patients presenting with non cardiac chest pain due to PD and/or depression experience an acute panic attack in a controlled setting, which is of high educational value. As a consequence, patients are more willing to accept a psychiatric diagnosis as explanation for their somatic complaints.

CONCLUSION

The CO_2 challenge test is a safe, simple and short lasting clinical test for diagnosing panic disorder driven chest pain. It can be used following screening with the HADS. A score of >8 on the HADS is the first step in finding patients with PD driven non cardiac chest pain. The next step is a CO_2 challenge. The high specificity of the (diagnostic) CO_2 challenge is additional to the high sensitivity of the (screening) HADS. This 2 step screening procedure is valuable, as patients with a high likelihood for PD and/or depression are filtered out of a large population with non cardiac chest pain. The CO_2 challenge can be used to reproduce complaints. Recognition of symptoms by the patient can thereafter be related to PD. Since PD is a treatable condition, patients should be referred to a psychiatrist for psychiatric treatment. The success rate of treatment with a serotonin reuptake inhibitor is 70%-80% [25]. Adequate treatment for PD related chest pain and/or palpitations of non cardiac origin may prevent chronic chest pain complaints with all its consequences for the patient's general health, cardiac prognosis, quality of life and health care costs.

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PART C | *biological issues*

8

8 |

Beta-thromboglobulin and Platelet Factor 4 levels
in postmyocardial infarction patients with major depression

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ABSTRACT

Platelet factor 4 (PF4) and beta-thromboglobulin (ß-TG) were studied in 12 depressed post-myocardial infarction (MI) patients and 12 matched non-depressed post-MI patients. PF4 was significantly higher in the depressed group than in the non-depressed group. ß-TG was increased in the depressed subgroup, but the difference was not statistically significant.

INTRODUCTION

The presence of elevated plasma concentrations of platelet-derived substances is an indicator of enhanced blood platelet activity in patients with myocardial infarction (MI) and

in patients with stable coronary artery disease (CAD) [1, 2]. In 1981, Levine et al. found a significant increase in plasma Platelet Factor 4 (PF4) concentration in patients with documented CAD [3]. Smitherman et al. described an elevation of ß-thromboglobulin (ß-TG) in patients with MI [4].

Increased plasma levels of PF4 and ß-TG were found in 21 depressed patients with ischemic heart disease (IHD) compared to eight non-depressed patients with IHD and 17 control subjects [5]. Depression occurs in 30% of patients after MI and is a significant risk factor for cardiac death in patients with IHD. Platelet-related abnormalities, which are present in depression, may be one of the links between depression and poor prognosis in depressed cardiac patients [6]. We investigated whether platelet function is increased in depressed patients with a first MI, using PF4 and ß-TG as markers, compared with a group of non-depressed post-MI patients matched for age, sex and size of MI.

METHODS

Patients with a major depression (MD), diagnosed according to DSM-IV criteria, after a first MI were compared with patients without MD after MI, matched for age, sex and size of MI (measured by peak value of aspartate amino transferase (ASAT)). Between 3 and 6 months after the first MI, blood was drawn for assay of PF4 (normal value 0–5 IU/ml) and ß-TG (normal value 10–40 IU/ml). Patients were not using anti-depressant medication. We based our small sample size on other studies that found a clear difference between heterogeneous groups, and expected at least similar results in a homogeneous and matched group.

Blood samples were taken in the morning hours at the coagulation laboratory of the University Hospital Maastricht. Patients were instructed to abstain from food, drinks and tobacco, starting the night before at 00:00. Blood was drawn by venipuncture without stasis from the antecubital vein with a butterfly infusion set using an open system after a 15-min resting period in a chair. Three samples were taken using different tubes: an ethylenediaminetetra-acetic acid (EDTA) tube followed by a draw tube containing a buffered tri-sodium citrate solution with theophylline, adenosine and dipyridamole (CTAD) and a citrate tube, 10 ml 3.8% (Becton Dickinson Vacutainer Systems Europe, Meylan, France). Immediately after sampling, CTAD and citrate tubes were centrifuged for 5 min at 2200xg at 18°C. Platelet-poor plasma was pipetted into another tube and centrifuged for 10 min at 10 000xg at 18°C. Plasma samples were stored at –70°C until analysis. Asserachrom PF4 and

ß-TG enzyme immunoassay kits (American Bioproducts, Parsippany, NJ, USA) were used for the determination of PF4 and ß-TG.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS). P-values were two-sided and a P-value ≤ 0.05 was considered as statistically significant. Non-parametric tests (Mann–Whitney U test) using PF4 and ß-TG as dependant variables were performed.

RESULTS

Ten men and two women were included in the depressed group as well as the non-depressed group. Mean age was 48.0±8.0 years (range 37–63) in the depressed group and 49.8±8.3 years (range 38–63) in the non-depressed group. Eleven patients in the non-depressed group used aspirin and one patient used coumarin. In the depressed group, all patients used aspirin. In the non-depressed group, there were three smokers compared to five smokers in the depressed group. Mean body weight in the depressed group was 75.7±8.5 kg vs. 84.7±14.4 kg in the non-depressed group (P=0.07). In the depressed group, one patient was known to have hypertension; in the non-depressed group, six patients were hypertensive. All patients were treated with antihypertensive medication. Baseline data are shown in table 1. There were no patients with diabetes, renal or hepatic failure. PF4 was significantly higher in depressed post-MI patients compared to non-depressed post-MI patients: mean rank 15.75 IU/ml vs. mean rank 9.25 IU/ml (P=0.02). There was a trend towards a significantly increased ß-TG level: mean rank 15.04 IU/ml vs. mean rank 9.96 IU/ml (P=0.08) (table 1). Non-depressed patients used more angiotensin converting enzyme (ACE) inhibitors and more nitrates (table 1). Whether this has implications for platelets or coagulation is not clear.

DISCUSSION

In this pilot study, PF4 was significantly higher in depressed post-MI patients compared to non-depressed post-MI patients and there was a trend towards increased ß-TG levels. Findings have to be interpreted with caution because of the small sample size, but the re-

TABLE 1 | Baseline characteristics of the depressed (n=12) vs. non-depressed post-MI patients (n=12)

	Depressed n=12	Non-depressed n=12
	Mean (S.D.)	Mean (S.D.)
ß-TG (IU/ml)	61.17 (47.98)	36.17 (15.09)
PF4 (IU/ml)	12.17 (11.30)	5.36 (4.91)
Blood platelets	255 (54.5)	218 (61.3)
Age	48.0 (7.98)	49.8 (8.34)
Body weight (kg)	75.7 (8.5)	84.7 (14.4)
Height (cm)	171 (7.6)	176 (6.1)
ASAT (U/l)	207 (163)	202 (125)
Males	10	10
Aspirin	12	11
Coumarin	0	1
ß-blocking agents	9	11
Calcium antagonists	2	4
Nitrates	1	4
ACE-inhibitors	4	9
Statins	11	11
Glucose (mmol/l)	6.43 (1.10)	7.43 (3.10)
Cholesterol (mmol/l)	5.04 (1.06)	4.46 (0.90)
HDL (mmol/l)	1.28 (0.46)	1.07 (0.28)
LDL (mmol/l)	2.92 (0.87)	2.55 (0.99)
Triglycerides (mmol/l)	2.16 (0.98)	2.14 (0.77)
Smoking	5	3
Hypertension	1	6

Data are presented as mean (SD); ß-TG = beta-thromboglubulin; PF4 = platelet factor 4; ASAT = aspartate amino transferase; HDL = high density lipoproteins; LDL = low density lipoproteins.

sults are in line with other studies, especially given the fact that we studied a very homogeneous group. Compared to the data from Laghrissi-Thode et al.[2], all but one of our patients used aspirin in a dose of 80 mg vs. a mean dose of 325±77 mg in the Laghrissi-Thode sample. This means that the differences in PF4 and ß-TG values in depressed vs. non-de-

pressed patients are not influenced by dosage of aspirin, as the same results were found for both studies.

Another difference with the Laghrissi-Thode study is that we only examined patients with a first MI, while Laghrissi-Thode had a very heterogeneous group consisting of CAD patients. An important finding is that despite the usage of aspirin in all our patients, a clear difference was found between groups. This is the first study to compare two homogeneous groups both using the same dosage of aspirin. To our knowledge, there are no studies investigating the efficacy of aspirin dosage in depressed post-MI patients. If confirmed in a larger cohort, the implication of our findings could be that aspirin is not that effective in depressed post-MI patients. Artifacts due to in vitro platelet activation are unlikely, as blood samples were taken under optimal and similar conditions using international guidelines [7].

Explanations for these findings are still speculative, but serotonin, abundantly present in platelets, might be the link in this association. In CAD, increased amounts of serotonin in coronary sinus blood are present [8]. Increased plasma concentrations of epinephrine and serotonin have been reported in depressed patients, as well as increased 5-HT_2 binding density [5]. Therefore, depressed patients may be at increased risk of serotonin-mediated platelet activation and coronary vasoconstriction. Recently, Musselman et al. found that the treatment of depression with a serotonin re-uptake inhibitor results in a normalization of platelet activation, including a decrease of PF4 and ß-TG [9]. This underlines a possible pathophysiologic role of serotonin in the increased cardiac morbidity and mortality of depression.

CONCLUSION

PF4 and ß-TG are increased in post-MI depression, in spite of the use of aspirin. It is hypothesized that this might be a pathophysiological link for depression post-MI as a risk factor for cardiac death. As anti-depressants seem to reverse this coagulation process [9], a different anti-coagulant therapy may be warranted in depressed post-MI patients. Prospective studies on blood platelet functioning in depressed post-MI patients can possibly shed more light on this important problem.

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9

9

A pilot study of platelet activation in non cardiac chest pain: *the role of panic disorder and depression*

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submitted

ABSTRACT

Background: Panic disorder (PD) is often found in patients presenting to Emergency Departments with non cardiac chest pain (NCCP). Prevalence rates range between 16% and 75%. Depression and anxiety are highly co-occurent disorders with similar pathophysiological mechanisms, and prognostic indicators for increased cardiac morbidity and mortality. This is possibly related to activated blood platelets, which release substances such as Beta-thromboglobulin (ß-TG), Platelet Factor 4 (PF4), sCD40L and serotonin (5HT). Serotonin metabolism is one of the key factors in the pathophysiology of depression and anxiety. However, 5HT levels are not different between patients with PD and/or depression and controls. Increased levels of 5HT are associated with coronary artery disease and occur-

rence of cardiac events. As yet, blood platelet function has not been studied in PD and/or depression driven NCCP. We hypothesized that (i) PF4, ß-TG and sCD40L are higher in patients, and (ii) peripheral 5HT levels are not different between controls and patients.
Methods: Study population: patients with NCCP diagnosed with PD and/or depression. The control population consists of subjects with NCCP without a psychiatric diagnosis.
Results: The study population consisted of 49 patients and 18 controls. There were no statistically significant differences between both groups as far as ß-TG, PF4, serotonin, and sCD40L is concerned.
Conclusion: PF4, ß-TG, 5HT and sCD40L levels were not different between patients and controls in this pilot study. In PD and/or depression driven NCCP, blood platelet activation does not seem to play a major role. However, our results should be replicated in a larger sample size.

INTRODUCTION

Each year more than 6 million patients in the United States present to Emergency Departments with chest pain suggestive of myocardial ischemia [1]. A large part of this group is hospitalized, but cardiac etiology is found in less than one-third [2]. Panic disorder (PD) is often found in patients presenting with chest pain; prevalence ranges between 16% and 75% with a mean of 31% [3]. These patients impose a large burden on the health care system, due to a high level of health care consumption [4, 5].

The co-occurrence of PD and depression is high. Approximately 50-60% of patients with major depression report a lifetime history of anxiety disorders such as PD [6]. Anxiety has been proven to be a cardiac risk factor in subjects without complaints and without documented coronary artery disease (CAD) [7, 8]. Also, anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients [9-11]. A pathophysiological link between anxiety, depression and cardiac morbidity as well as mortality could lie in blood platelet function.

Several biomarkers resulting from in vivo activation of blood platelets are Platelet Factor 4 (PF4), Beta-Thromboglobulin (ß-TG) and serotonin (5HT). Platelet activation and thrombosis are important components of atherosclerosis [12]. PF4 and ß-TG are increased in depression post-myocardial infarction (MI) [13-16].

CD40L is the ligand of CD40, a membrane glycoprotein [17]. Soluble CD40 Ligand (sCD40L) is expressed on platelets and released on activation. The CD40L-CD40 system

may be regarded as a marker for plaque and platelet activation [18]. However, no information is yet available on the relationship between sCD40L and psychiatric disorders such as depression or PD. As it has been shown that ß-TG and PF4 are related to depression, one could expect that sCD40L, which comes also from α-granules, could be involved in depression and/or anxiety driven blood platelet activation. Recently, increased levels of sCD40L have been shown to be an important marker for cardiac events [16, 19-22].

Serotonergic mechanisms involved in poor cardiac prognosis could be serotonin mediated vasoconstriction, growth-promoting effects on vascular smooth muscle cells and endothelial cells, and promoting release of other substances from blood platelets associated with aggregation [23].

Serotonin has been described as one of the key factors in the pathophysiology of depression and anxiety [24-26]. However, peripheral baseline values of 5HT are not different between patients with depression and/or PD and controls [27].

Several studies related psychological factors to cardiovascular events [18, 28, 29]. Platelet activation has been described as an important pathophysiological link in the relationship between depression and increased mortality and morbidity in cardiac patients [15, 29-32]. We wanted to investigate whether there was enhanced platelet activation in patients with PD and/or depression driven NCCP. We therefore developed the following hypotheses:

(i) PF4, β-TG and sCD40L are higher in patients compared to controls, and

(ii) 5HT is not different between controls and patients.

METHODS

Subjects

The study population consisted of consecutive patients presenting with chest pain to the First Heart Aid (FHA) of the University Hospital Maastricht. Data collection was done in the period September 2000-December 2002. Patients were recruited from a larger study, details of the screening methods have been published elsewhere [33].

Patients with NCCP and a score ≥ 8 on the depression and/or anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) participated in a structured psychiatric interview (Mini International Neuropsychiatric Interview [34]) based on the Diagnostic and Statistical Manual (DSM IIIR). Patients suffering from dementia, living more than 50 kilometres from the hospital or not speaking the Dutch language were excluded, as well as pa-

tients with renal or hepatic failure (defined as values >3x upper limit). All participating patients signed an informed consent form. The local ethical committee approved the study.

Parallel to this patient group, a consecutive cohort of NCCP patients scoring <8 on either HADS subscale was included in the study, serving as reference group of NCCP patients with low levels of anxiety and/or depression and no psychiatric diagnosis.

Blood sampling

A blood sampling appointment was scheduled after the MINI was performed.

Blood samples were taken between 08.30 and 10.30 AM. In order to minimize in vivo platelet activation patients had to rest 15 minutes before blood collection. A venipuncture was performed after an overnight fast, applying minimal stasis, in the antecubital vein. Blood samples were collected using a 19-gauge needle and Vacutainer tubes (Becton-Dickinson, Basel, Switzerland). The first 4 ml blood was collected in ethylene diamine tetra acetic acid (EDTA) tubes to assess blood platelet count. The next 4,5 ml were collected in tubes containing an anticoagulant and antiplatelet cocktail consisting of citric acid, theophylline, adenosine, and dipyridamole (CTAD) to minimize platelet activation in vitro. The tube was filled to capacity and gently inverted to ensure complete mixing with the anticoagulant. Samples were first centrifuged at 2200g for 5 minutes. The plasma thus obtained was subsequently centrifuged at 10.000 g for 10 minutes at 18°C. Blood samples for measurement of sCD40L in plasma were collected in EDTA tubes (Becton-Dickinson, Basel, Swiss) and centrifuged at 2200g for 5 minutes [35]. Whole blood for serotonin analyse was also collected in EDTA tubes. Whole blood and plasma samples were stored at -70°C until analysis.

Laboratory analysis

Concentrations of β-TG and PF4 were measured in one batch using commercially available, high sensitivity enzyme-linked immunoabsorbent assays (Asserachrom, Roche). Normal values are 0-5 IU/ml for PF4 and 10-40 IU/ml for β-TG.

Plasma sCD40L concentrations were measured by ELISA (Bender MedSystems BMS239MST). The detection limit of this assay was 0.160 ng/ml.

Whole blood for determination of serotonin was deproteinized as described [36] with the exception that N-methyl-5-hydroxytryptamine was used as an internal standard [37]. The supernatant was subjected to high performance liquid chromatography using fluorogenic detection and gradient elution [38]. Linearity was well beyond 10 µM. Within-assay CV was 5.3% and between-assay CV was 7.3%.

TABLE 1 | Characteristics of patients and controls

	Controls n=18	Patients n=49	p-value
Gender % Male Female	 44.4 55.6	 57.1 42.9	ns
Age	62.67 ± 11.40	58.35 ± 12.77	ns
Length in cm	168.56 ± 6.96	171.73 ± 8.64	ns
Weight in kg	77.42 ± 10.90	79.02 ± 18.74	ns
BMI	27.15 ± 3.43	26.60 ± 4.75	ns
Smoking yes %	22%	39%	ns
ASA	33%	25%	ns
Oral anticoagulants	11%	4%	0.002
Statins	67%	25%	0.003
Betablocking agents	61%	45%	ns
Calcium Antagonists	11%	20%	ns
Ace-inhibitors	22%	8%	ns
Nitrates	28%	16%	ns
A2 antagonists	11%	8%	ns
Depression	0%	2%	<0.0001
Panic disorder (PD) (n)	0%	27% (13)	<0.0001
Depression and PD (n)	0%	71% (35)	<0.0001
Cardiac history Yes % (n) No % (n)	 50% (9) 50% (9)	 44.9% (22) 55.1% (27)	ns
Creatinin	n.a	82.98 ± 19.05	
Hypertension Yes No unknown	 44.4% 44.4% 11.1%	 40.8% 46.9% 12.2%	ns

BMI = Body Mass Index, ASA = Acetyl salicylic Acid, PD = Panic Disorder,
HADS = Hospital Anxiety and Depression Scale, Na = Not available
Data are presented as mean percentages and (n) where applicable. Other data are presented as mean ± SD.

Statistical analysis

Baseline characteristics were investigated for patient and control group. In case of dichotomous variables the chi-square test was used. In case of continuous variables indepen-

TABLE 2 | **Biomarkers for controls versus patients**

Variable	Controls n=18	Patients n=49	P
ß-TG IU/ml	29.33 ± 9.6	30.61 ± 10.8	ns
PF4 IU/ml	0.91 ± 1.41	1.06 ± 1.73	ns
Serotonin micromol/L	1.26 ± 0.51	1.13± 0.70	ns
Serotonin / Platelet ratio	5.48 ± 1.91	4.69 ± 2.62	ns
sCDL40	0.09 ± 0.21	0.05 ± 0.14	ns
Blood platelets	226.44 ± 36.07	243.82 ± 59.61	ns

Data are expressed as mean ± SD

PF4 = Platelet Factor 4, ß-TG = Beta-thromboglobulin, NS = Not significant

dent Samples T-tests were applied. Extreme outlying values (>3x SD) were excluded and scatter plots were used for visual inspection. These cases were excluded for further analysis. Oneway ANOVA was performed to investigate confounding factors. Pearson correlations were performed for the relationship between statine-use and smoking, as well as for the correlation between HADS score and platelet activation markers. The significance level was set at 0.05 (two tailed). Statistical analyses were performed with SPPS release 11.0 for Apple Macintosh.

RESULTS

The patient group consisted of 54 patients. Two patients were excluded due to sampling errors. Three patients were extreme outliers (>3x SD) and not included in the analysis. The final baseline sample consisted of 49 patients, the control group of 18 subjects. Baseline characteristics are given in table 1. Patients were not different from controls as far as age, gender, previous cardiac history, BMI and smoking is concerned. Patients used less statines (25% versus 61%, p=0.003) and acenocoumarol (4% versus 11%, p=0.002) than controls. As the presence of a previous cardiac history was equally divided over both groups, we have no explanation for this finding, which may be coincidental. Aspirin-use was not statistically significant between both groups. Neither patients nor controls had hepatic or kidney failure.

The differences of PF4 and β-TG values between controls and patients were not statistically significant (table 2), which is contrary to our hypothesis. The same goes for sCD40L.

Table 1 shows that the control group used statistically significant more statines compared to the patient group. However, neither One way ANOVA nor Pearson correlations identified statine-use as a confounder [19, 21].

In line with our hypothesis, we did not find any statistically significant differences in the values of 5HT between controls and patients.

DISCUSSION

To our knowledge, this is the first study to evaluate blood platelet function using PF4, β-TG, sCD40L and 5HT in a clinical sample of patients presenting with PD and/or depression driven NCCP.

PF4 and β-TG

Contrary to our expectations, no differences in β-TG and PF4 were found between patients and controls. Assuming that psychiatric symptoms play a role, rather than a DSM diagnosis, we investigated whether there was a correlation between severity of symptoms (as measured by the HADS) and platelet activation markers. However, when putting both groups together, no correlation was found between the biological markers and psychiatric symptoms. This seems to indicate that blood platelet function (measured by PF4, ß-TG and sCD40L) plays no major role in the pathophysiological link between increased cardiac morbidity and mortality and affective disorders, although we did not yet study cardiac outcome in our population.

One could also suggest that the composition of our control population might not be appropriate for this matter, as these patients also presented with NCCP, but without symptoms up to a level of a psychiatric diagnosis.

In a previous study in first MI patients, we did find higher values of PF4 and a trend for β-TG in the depressed group compared to the non-depressed group [13]. This was also found by other authors [14, 15]. These previously found elevated values might be due to the 'recent' cardiovascular event. β-TG and PF4 values of the non-depressed post MI group were higher than in our current depressed/PD group [13]. That suggests that PF4 and ß-TG increases are more likely to be due to cardiac events rather than to psychiatric disorders.

It is not expected that the pathophysiology in depression is different compared to PD, as 71% of our group had PD as well as depression. The presence of a previous cardiac history was also equally distributed over patients and controls, thus excluding any bias in this matter.

Serotonin

It has been shown previously that baseline values of 5HT are not different between healthy subjects and patients with PD and/or depression [27]. We therefore expected no differences between both groups. This was confirmed: our findings are in line with previous studies.

sCD40L

To our knowledge, sCDL40 has not been investigated before in psychiatric populations. We found no statistically significant differences between patients and controls (0.09 ± 0.21 vs. 0.05 ± 0.14, p=ns)

CONCLUSION

We found in our pilot study that ß-TG, PF4, sCD40L and 5HT were not different between patients with PD and/or depression driven NCCP and controls. These findings, however, should not be generalized. The strength of our pilot study is that patients as well as controls underwent a MINI. On the other hand, our sample size is not very large. Another factor might be that our control group has not the appropriate composition, as its subjects also presented with NCCP, but without a psychiatric diagnosis. In future studies, healthy age- and gender-matched controls should be added.

Therefore, replication of our findings should be confirmed in larger sample sizes on the one hand, using 'real' healthy controls on the other. As yet, blood platelet function does not seem to play an important role between increased cardiac morbidity and mortality in anxiety and/or depression driven NCCP. Other mechanisms that may be involved are poly-unsaturated fatty acids, which also have been investigated by our group.

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A pilot study of PUFA's in non cardiac chest pain: *the role of panic disorder and depression*

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ABSTRACT

Background: Chest pain of non cardiac origin is common in patients presenting to Emergency Departments and often due to panic disorder (PD). Anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients. Panic like anxiety has also been proven to be an independent risk factor for cardiovascular death, especially sudden cardiac death. A decrease in omega-3 polyunsaturated fatty acids (PUFA's) has been associated with cardiac mortality and affective dysregulation.

Therefore one of the mechanisms of PD related mortality-increase might be changes in PUFA levels. We hypothesised that omega 3 PUFA levels are decreased and omega 6 PUFA levels are increased in patients with PD and/or depression driven chest pain.

Method: PUFA status was measured in phospholipids of 54 patients suffering from PD and/or depression driven chest pain and 20 patients with non cardiac chest pain without a psychiatric diagnosis.
Results: Omega 3 was decreased in the PD/depression group, while omega 6, omega 6/3 ratio and AA/EPA ratio were increased in the PD/depression group compared to the non PD/depression group.
Conclusion: To our knowledge, this is the first study to investigate the relationship between PUFA's and PD and/or depression driven non cardiac chest pain. Non cardiac chest pain patients suffering from PD and/or depression have lower omega 3 PUFA levels and elevated omega 6 PUFA levels. These findings might play a role in the fact that anxiety and sudden cardiac death are related.

INTRODUCTION

Chest pain or palpitations of non cardiac origin are common in patients presenting to Emergency Departments (ED) and outpatient clinics. Half of the patients presenting in a multidisciplinary chest pain unit without coronary artery disease (CAD) have active gastro-esophageal or anxiety disorders [1]. Panic disorder (PD) is an anxiety disorder often found in patients presenting with chest pain; prevalence of PD in an ED setting ranges between 16% and 75% with a mean of 31% [2]. PD has important consequences for the health care system, including risk of frequent hospital admissions, unnecessary diagnostic investigations and iatrogenic complications [3]. In addition, quality of life is markedly decreased in chest pain patients with PD [4]. The co-occurrence of PD and depression is high: approximately 50-60% [5]. Anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients [6, 7]. Anxiety is related to sudden cardiac death (SCD) with an odds ratio of 4.46 [8]. There is also an association between phobic anxiety and fatal CAD [9]. Panic like anxiety has also been proven to be an independent risk factor for cardiovascular death, especially SCD [10].

In recent years, there has been a growing body of evidence that n-3 polyunsaturated fatty acids (PUFA's) can prevent SCD [11-14]. Also in patients having no clinical evidence for CAD, an increase in n-3 PUFA's diminishes the risk for SCD [11]. Depressed patients show significant depletion of total n-3 PUFA's in cell membranes from red blood cells [15] and in plasma phospholipids [16]. The most described PUFA's are arachidonic acid (AA), Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), omega 3/omega 6 ratio [14, 17, 18].

Based on these findings, the following hypotheses were formulated:

1. Omega 3 PUFA levels are decreased in patients presenting with non cardiac chest pain (NCCP) suffering from PD and/or depression.
2. Omega 6 PUFA levels, AA/EPA ratio and omega 6/omega 3 ratio are increased in patients presenting with NCCP suffering from PD and/or depression.

METHODS

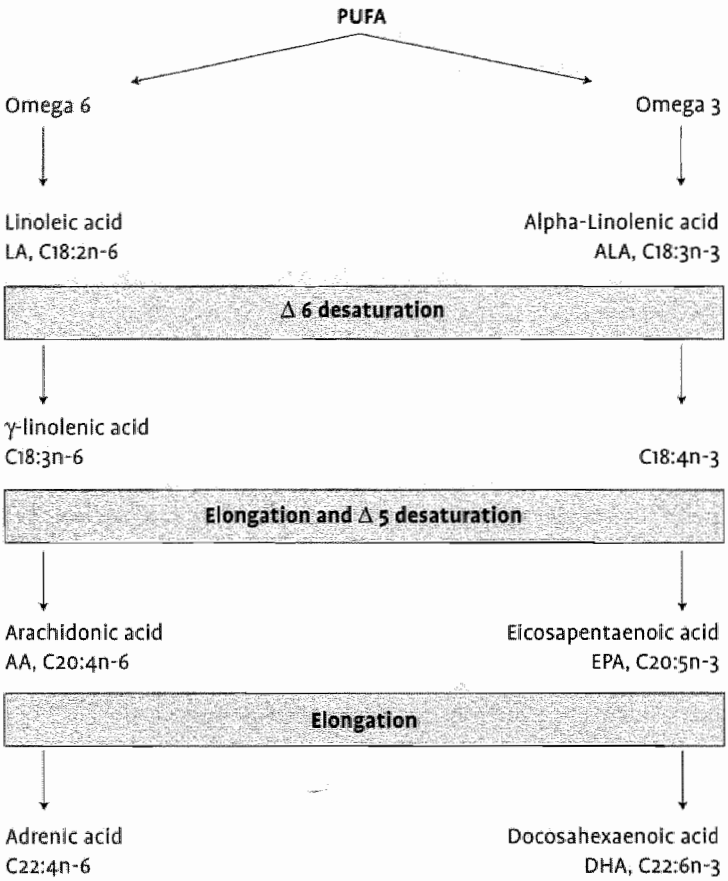
Essential PUFA's

PUFA's can be divided in 2 main classes: the omega-6 (or n-6) class and omega-3 (or n-3) class (figure 1). N-6 is mostly present in vegetable oils, n-3 in fish [12]. These PUFA's are 'essential' because we are unable to make them ourselves [13]. The n-3 PUFA α-linolenic acid (ALA, C18:3n-3) and the n-6 PUFA linoleic acid (LA, C18:2n-6) are the predominant essential fatty acids in humans and the parent fatty acid of their class [13, 19]. LA can be elongated and desaturated into arachidonic acid (AA, C20:4n-6) via Δ 6 and Δ 5 desaturase. ALA is elongated and desaturated in Eicosapentaenoic acid (EPA, C20:5n-3) and in Docosapentaenonic acid (DPA, C22:5n-3). EPA and docosahexaenoic acid (DHA, C22:6n-3) are the major N-3 PUFA's found in cold water fish and responsible for the cardioprotective effect [19] (figure 1). Dihomo gamma linolenic acid (DGLA, C20:3n-6) is the precursor for Prostaglandin E1 (PGE1) while AA is the precursor for PGE2 [20]. PGE2 and PGE1 are capable of inhibiting the release of stress hormones e.g. (nor)epinephrine and serotonin [20]. As zinc is involved in FA metabolism, it is also included in the analysis. The desaturase enzymes (Δ 6 and Δ 5 desaturase) require zinc (Zn) as co-factor [16].

Subjects

The study population consisted of patients presenting with chest pain and/or palpitations to the First Heart Aid (FHA) of the University Hospital Maastricht. This is an annex to the ED specifically dedicated to patients presenting with cardiac complaints. Data collection was done in the period September 2000-December 2002. Patients were recruited from a larger study, details of the screening methods have been published elsewhere [21]. Patients with chest pain of non cardiac origin and a score $\geq$ 8 on the depression and/or anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) participated in a structured psychiatric interview (Mini International Neuropsychiatric Interview). Patients suffering from dementia, living more than 50 kilometres from the hospital or not speaking

FIGURE 1 | Pathways for the desaturation and elongation of n-3 and n-6 PUFA's



the Dutch language were excluded. All participating patients signed an informed consent form. Parallel to this patient group reporting symptoms of anxiety and/or depression, a consecutive cohort of NCCP FHA patients scoring < 8 on either HADS subscale was included in the study as reference group of chest pain patients with low levels of anxiety and/or depression. The local ethical committee approved the study.

Blood samples

After patients were diagnosed with PD and/or depression (patient group) or no psychiatric diagnosis (controls), blood sampling was performed as soon as possible, but within maximally one week after the interview.

Blood samples were taken between 08.30 and 10.30 AM after an overnight fast. A venipuncture was performed in the antecubital vein. Blood samples were collected and stored in sterile Vacutainer tubes without additives (Becton-Dickinson, Basel, Switzerland). Samples were immediately centrifuged at 2200 x g for 5 minutes. Serum thus obtained was stored at -70°C until analysis.

Laboratory analysis

A single operator, using the same batch of reagents, carried out all assays of serum fatty acids. The fatty acid composition was measured by gas chromatography and expressed as a percentage of total fatty acid content in phospholipids. Serum Zn was determined on a Perkin-Elmer Analyst 800 atomic absorption spectrometer using an air-acetylene burner system. The following saturated fatty acids (SAFA's), monounsaturated fatty acids (MUFA's), polyunsaturated fatty acids (PUFA's) and dimethyl-aldehydes (dma) were measured in the phospholipids fraction: total amount of fatty acids, c14:0, c15:0 , c16:1w7, c16:0, c16:0DMA, c17:0, c18:3w6, c18:2w9, c18:2w6, c18:3w3, c18:1w9, c18:1w7, c18:0, c18:1DMA, c18:0DMA, c20:4w6, c20:3w6, c20:5w3, c20:3w9, c20:4w3, c20:2w6, c20:3w3, c20:1w9, c20:1w7, c20:0, c22:5w6, c22:6w3, c22:4w6, c22:5w3, c22:3w9, c22:2w6, c22:3w3, c22:1w9, c22:0, c23:0, c24:0, c24:2w6, c24:1w9. The sums (Σ) of the percentages of omega-3 and omega-6 FA's were computed as well as the omega-6/omega-3 ratios, AA/EPA index, essential fatty acid index (EFA) and the EFA deficiency index (EFADI).

A total omega 6/3 ratio was calculated (ratio n6/n3 complete) as well as an omega 6/3 ratio using only those omega 3 and 6 PUFA's of which the value was more than 0,1% of the total PUFA value (omega 6/3 ratio adapted). (LA+ALA)/(AA+EPA) ratio is used as an index of Δ 6 and Δ 5 desaturase [20].

Statistical analysis

Results are expressed as means±standard deviations. Analyses were performed using Statistical Package for Social Sciences (SPSS) release 11.0 for Apple Macintosh. Differences between groups were analysed using independent sample t test for continuous variables and Chi square test for dichotomous variables. One-way ANOVA was performed to investigate confounding factors. The significance level was set at 0.05 (two tailed).

TABLE 1 | **Characteristics of the patient and control group**

	Controls n=20	Patients n=54
Gender %		
Male	45	55.6
Female	55	44.4
Age mean ±SD	61.15 ± 14.01	58.74 ± 12.88
Length in cm mean ±SD	169 ± 7	171.26 ± 8.52
Weight in kg mean ±SD	78.08 ± 13.48	78.28 ± 18.16
Smoking yes	20%	37% *
ASA	30%	27.8%
Anticoagulants	10%	3.7%
Statins	65%	27.8% *
Betablocking agents	55%	42.6%
Calcium Antagonists	15%	24.1%
Ace-inhibitors	20%	7.4%
Nitrates	25%	16.7%
A2 antagonists	15%	9.3%
Depression	0%	70.4% *
Panic disorder (PD)	0%	98.1% *
Depression and PD	0%	68.5% *
Cardiac history		
Yes (n)	9	27
No (n)	11	27

* = $p<0.05$ compared to control group

RESULTS

The PD and/or depression group consisted of 54 patients. The control group consisted of 20 patients. As shown in table 1, baseline characteristics revealed more smokers in the patient group compared to the control group (37% versus 20%, p= 0.026). The control group used significantly more cholesterol lowering medication (statins) compared to the patient group (65% vs. 27.8%, p=0.01).

Data concerning the PUFA's are shown in table 2.

The total percentage of omega 6 FA's was higher in the patient group compared to the con-

TABLE 2 | **PUFA's and ratios for controls and patients**

	Controls n=20	Patients n=54
Total	1427.02	1449.56
c18:2w6 % * (LA)	19.11 ± 2.48	20.50 ± 2.23 *
c18:3w3 % (ALA)	0.192 ± 0.06	0.211 ± 0.06
c20:4w6 % (AA)	9.711 ± 2.20	9.20 ± 1.90
c20:5w3 % (EPA)	1.05 ± 0.86	0.87 ± 0.52
c22:5w6 % (DPA)	0.17 ± 0.08	0.17 ± 0.06
c22:6w3 % (DHA)	3.764 ± 0.98	3.33 ± 0.88
Omega 3 total %	6.03 ± 1.71	5.44 ± 1.31
Omega 6 total %	33.04 ± 2.08	34.0 ± 1.76 **
Omega 7 total %	2.12 ± 0.33	1.98 ± 0.26
Omega 9 total %	10.39 ± 1.06	10.20 ± 1.00
Ratio omega 3/omega 6	0.186	0.162
Σ SAFA %	47.21 ± 0.81	47.17 ± 0.96
Σ MUFA %	12.49 ± 1.07	12.14 ± 1.14
Σ PUFA %	39.04 ± 1.45	39.41 ± 1.11
Σ n-6 LPC %	13.30 ± 2.31	12.89 ± 1.98
Σ n-3 %	5.80 ± 1.69	5.20 ± 1.29
EFA	3.16	3.27
EFADI	0.014	0.013
AA/EPA	12.09	13.87
Ratio omega 6/3 complete	5.843	6.602
Ratio omega 6/3 adapted	5.863	6.621
Zinc	92.54	97.73

Data are presented as mean ± SD

* = p-value 0.024 controls versus patients ** = p-value 0.050 controls versus patients

trols (34.0±1.76 vs. 33.04±2.08, p<0.05). Omega 3 levels were slightly lower in the patient group (5.44±1.31) compared to the control group (6.03±1.71), though not statistically significant. In patients, the AA/EPA ratio was increased as well as the omega 6/omega 3 ratio. However, due to outlying values differences were not statistically significant.

Linoleic Acid (C18:2w6) was significantly higher in the patient group compared to the controls (20.50± 2.23 vs. 19.11± 2.48; p=0.024).

The average plasma zinc was increased in the patient group compared to the control group (97.7 ± 10,6 vs. 92.5 ± 9,3; p=ns).

DISCUSSION

To our knowledge, this is the first study to investigate the relationship between PUFA's and PD and/or depression driven NCCP.

We found that in patients presenting with NCCP and diagnosed with PD and/or depression, omega 3 PUFA levels are decreased while omega 6 PUFA levels are increased. Therefore the omega 6/3 ratio as well as the AA/EPA ratio is increased in patients. This was in line with our hypothesis.

The results of the baseline PUFA findings in the depressed group are in line with previous findings [16, 22, 23].

Statins seem to play an important role in PUFA-metabolism. They enhance the conversion of LA to the long chain PUFA's such as AA [24]. In the control group, 65% of the subjects used statins compared to 27.8% in the patient group (p=0.01). As previous cardiac history was equally divided over both groups (table 1), we have no explanation for this finding, which may be coincidental. LA was lower (18.54) in the controls with statins compared to the controls without statins (20.17, p=ns). AA was higher in the controls with statins (10.09) compared to the controls without statins (9.01, p=ns). The same findings were seen in the patient group, although not that outspoken.

Of the total group of patients using statins (controls as well as patients, n=28), it appeared that LA was lower in the controls (18.54) compared to the patients (19.65) (p=ns). AA was lower in the patients (9.69) than in the controls (10.09)(p=ns). This could explain why the LA in the control group is lower compared to the patient group.

As stated earlier, AA is a precursor for PGE2 [20]. PGE2 can inhibit 5HT and epinephrine. PD patients show increased epinephrine release in urine, compared to control subjects [25]. One could suggest that control patients have lower epinephrine-release, maybe due to increased PGE2. One would hypothesize further that controls have therefore lower AA compared to patients. This is in line with our findings.

DHA is associated with a higher heart rate variability (HRV)[26]. As stated earlier, it is known that anxiety is associated with an increased risk for sudden cardiac death. Decreased HRV is suggested as an underlying mechanism. Therefore one would expect that, if the pathophysiological link between anxiety and mortality are PUFA's, DHA should be higher in

controls than in patients. Our findings show a trend towards a relationship (3.76±0.98 in controls vs. 3.33±0.88 in patients, p=0.07), but are not statistically significant.

The outcomes as far as Zinc is concerned are not in line with previous studies, showing decreased Zinc levels (as indicator of immune activation) in depressive patients [16, 27]. However, one could hypothesize that statins play a role also. Statins enhance the conversion of LA to the long chain PUFA's such as AA via Δ 6 and Δ 5 desaturase. These enzymes use Zinc as a cofactor, which could lead to more Zinc 'consumption', hence a lower Zinc value. As the control group used more statins, this could explain the lower Zinc levels in controls compared to patients. Another explanation could be that the pathophysiology in depression is not the same as in PD. This seems unlikely, however, as there is a high co-occurrence of depression and PD.

The PUFA changes found in this pilot study were collected from a small sample size and cannot be generalized. The findings of this pilot study should be replicated in a larger group as it may have clinical implications in the future in risk factor modification as far as cardiac morbidity and mortality is concerned in patients with psychiatric co-morbidity.

CONCLUSION

In patients with PD and/or depression driven non cardiac chest pain, omega 6 levels are increased. Omega 3 levels, AA/EPA and omega 6/3 ratio are decreased in patients compared to controls although statistically not significantly, probably due to the small sample size. Statins seem to interfere with PUFA metabolism. Our findings should be replicated in a larger sample.

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Epilogue and general discussion

Who's afraid of chest pain

The investigations reported in this thesis were inspired by my experiences working in a cardiology clinic. Each year, thousands of people come to see a cardiologist with chest pain or palpitations. Unfortunately, extensive and expensive non-invasive and invasive examinations and procedures with possible iatrogenic damageing consequences, do not give a satisfying cardiological explanation for everyone. A large group of patients continue to have complaints such as chest pain, despite the fact that no cardiac abnormality can be found.

This situation is undesirable for all parties involved. First of all for the patient, who remains feeling ill and searching for an explanation. Anxiety and frustration will grow as somatic diagnoses fail to be found. Furthermore for the cardiologist, who keeps on seeing the *same patient over and over again*, unable to offer proper care without a proper diagnosis. And finally for the health care system, as these patients are large consumers of medical facilities, placing a heavy burden on the health system, both time-wise and financially.

As this seemed to be a multidisciplinary problem, with other than somatic causes involved, we did our studies in close collaboration with the Department of Psychiatry. They began in 1994, when publications showed that depression after a myocardial infarction is common and leads to increased mortality. Originally, the Cardiopsychiatry research was directed towards patients with a depressive disorder after myocardial infarction. This research line was extended in 1999 to the field of anxiety and panic disorder (PD).

First of all we wanted to evaluate the magnitude of the problem in our own setting, that is a hospital with both an academic as well as a general medical function; the hospital being the only one in the city of Maastricht. This means that all patients of the region come to the First Heart Aid in case of cardiac complaints, resulting in a large and unselected

number of patients. A pilot study revealed the absence of a somatic explanation in many cases. We had identified an often occurring problem. The next step was a larger study with the aims to:

1. find diagnostic instruments,
2. investigate biological mechanisms and
3. evaluate treatment.

As to treatment, a randomised, double blind placebo and care-as-usual controlled trial with sertraline has been performed recently, the final results will soon be available. The data reported in this thesis came from the different areas of investigation. For that purpose, approximately 6000 FHA patients were screened in 2,5 years.

Chest pain and psychiatry

The apparently close link between chest pain and psychiatry is not that obvious (anymore) in modern medicine. In 1871, the 'Irritable Heart syndrome' was introduced as a term for a condition in which chest discomfort was caused by emotional upset. This was one of the first names from a long list for patients suffering from chest pain without a clear cause. Terms as 'folie cardiaque' suggested the link between cardiology and psychiatry [1]. Chest pain appeared to be a prominent symptom of anxiety, especially in panic disorder.

Panic disorder (PD) was recognized as a psychiatric syndrome with clear diagnostic criteria in 1980 in the Diagnostic and Statistical Manual (DSM) III. In 1994, the DSM IV criteria were adapted and they are currently in use. The definition of a panic attack is "a discrete period of intense fear or discomfort, in which at least 4 (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes" (see table 1).

The origin of 'panic' goes back to Greek mythology. Panic is named after the Greek god Pan. Pan was the god of nature, had legs resembling those of a goat and frequently took a nap in caves near the road. When disturbed during his sleep by passengers, he would scream intensely and bloodcurdling, thus causing an intense fear and often death of the passing travellers. This sudden, overwhelming terror or fright became known as 'panic' [3].

As stated earlier, chest pain is one of the symptoms of a panic attack. Chest pain is one of the major complaints in Emergency Department (ED) settings, while the diagnosis is often 'non cardiac chest pain' (NCCP) [4]. Causes of NCCP may be gastro-intestinal, pulmonary, musculoskeletal, vascular or drug-induced (for example cocaine)[5]. However, panic disorder (PD) is a frequent and often unknown cause as well.

Recently, Huffman reviewed studies published between 1970 and 2001 on the subject

TABLE 1 | **DSM-IV panic attack symptoms**

1.	Palpitations, pounding heart, or accelerated heart rate
2.	sweating
3.	trembling or shaking
4.	sensations of shortness of breath or smothering
5.	feeling of choking
6.	chest pain or discomfort
7.	nausea or abdominal distress
8.	feeling dizzy, unsteady, lightheaded or faint
9.	derealization (feelings of unreality) or depersonalization (being detached from oneself)
10.	fear of losing control or going crazy
11.	fear of dying
12.	paresthesias (numbness or tingling sensations)
13.	chills or hot flushes

Panic disorder (PD) is defined as:

1. recurrent and unexpected panic attacks
2. at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
   - persistent concern about having additional attacks
   - worry about the implications or consequences of the attack
   - a significant change in behaviour related to the attack
3. the panic attacks are not due to direct physiological effects of substances (eg drugs) or a general medical condition (eg hyperthyroidism) [2, 3]

of PD and chest pain [6]. It appeared that ± 25% of all patients who present with chest pain to an ED suffer from PD. PD prevalence rates vary between 22-59% in patients who have normal coronary arteries on coronary angiography or a normal thallium scintigraphy [1, 7-12]. In patients with proven coronary artery disease (CAD) prevalence ranges even more: between 22-59% [1, 9, 11, 12].

We found in our own pilot study (described in chapter 3) at the First Heart Aid (FHA) that 83% of 55 patients reporting chest pain, diagnosed with NCCP and scoring ≥ 8 on the Hospital Anxiety and Depression Scale (HADS) suffered from PD and/or depression [13]. The recognition of this problem by the cardiologist or cardiologist in training is very low and ranges between 2-13% [13, 14]. Recognition of psychological or psychiatric symptoms in our study was also low: in 13% (n=7) a diagnosis of 'hyperventilation' was made by the attending FHA physician. However, probably due to the fact that cardiologists were aware

of the study, the 13% recognition was higher than the 2% known from literature. It was remarkable that 5 of the 7 patients recognized by the cardiologist as having 'hyperventilation' suffered from both PD and depression. This underlines the findings by others that PD and depression are often occurring together [1, 2, 15].

Clinicians are generally not aware that psychiatric disorders such as PD or depression can present mainly with somatic symptoms. Panic attack symptoms are for instance chest pain, palpitations, sweating and shortness of breath [16]. Symptoms of angina pectoris due to myocardial ischemia may be chest pain, palpitations, sweating and shortness of breath. Chest pain is a very common (22%-70%) somatic symptom during a panic attack [6]. Therefore, patients present themselves in somatic settings, rather than in psychological or psychiatric settings.

In 1987, the concept of Non Fearful Panic Disorder (NFPD) was introduced by Beitman [17-19], and defined as intense episodes of discomfort without either fear of dying, going crazy or losing control, but including at least 4 other PD symptoms [19]. NFPD seems to be a variant of PD and has a chronic course similar to PD [19]. NFPD patients are older compared to PD patients, while PD generally originates in early adulthood [19].

Panic disorder and the cardiologist

This daily encountered problem of PD driven chest pain is a major challenge for the cardiologist, as it has several consequences. Firstly, PD is associated with substantial functional morbidity [1, 6, 19, 20]. "There's nothing wrong" does not reassure patients [21]. *Patients continue to have chest pain and their quality of life is markedly decreased* [22-26]. Secondly, it leads to a frequent use of health care resources [1, 27-29]. Often invasive diagnostic tests are performed such as coronary angiography with the risk of iatrogenic complications. But, again, a normal coronary angiography does not reassure the patient and they keep on having complaints [30].

The problem becomes even greater in patients who are diagnosed with CAD, but who may have PD at the same time! Prevalence of PD in CAD patients ranges between 34%-50% [9, 11]. We found in our sample that a substantial part (39%, 104 out of 266 patients) of patients presenting with NCCP and scoring ≥ 8 on either the anxiety or depression subscale of the HADS, had a previous cardiac history. The majority of this sample (73%) had a diagnosis of PD and/or depression [31]. This underlines the findings by other authors.

A third important issue of (unrecognized) PD in NCCP is mortality. Fleet reviewed the literature on cardiovascular death by panic-like anxiety [32]. It appeared that there is a link between panic-like anxiety and increased cardiovascular mortality. Kawachi found in

a prospective study in 34.000 males without coronary heart disease (CHD) at baseline, a strong causal relationship between phobic anxiety and fatal CHD. The relative risk of fatal CHD among men with the highest levels of anxiety was 3. When fatal CHD was divided into sudden and non-sudden cardiac death, the excess risk (relative risk 6) was confined to sudden death [33]. Recently, the association between phobic anxiety and risk of CHD and sudden cardiac death, has also been suggested in a large cohort of women [34]. Januzzi evaluated the influence of anxiety and depression on outcome in patients with CAD [35]. It appeared that there is strong epidemiological evidence that psychological factors such as anxiety and depression, have effects on the development of CAD and on sudden cardiac death [35].

Finally, patients with depression and/or anxiety have a reduced compliance with treatment, and often a less healthy life style due to smoking and avoidance of exercise out of fear for chest pain or palpitations [1, 21, 35].

A biological model

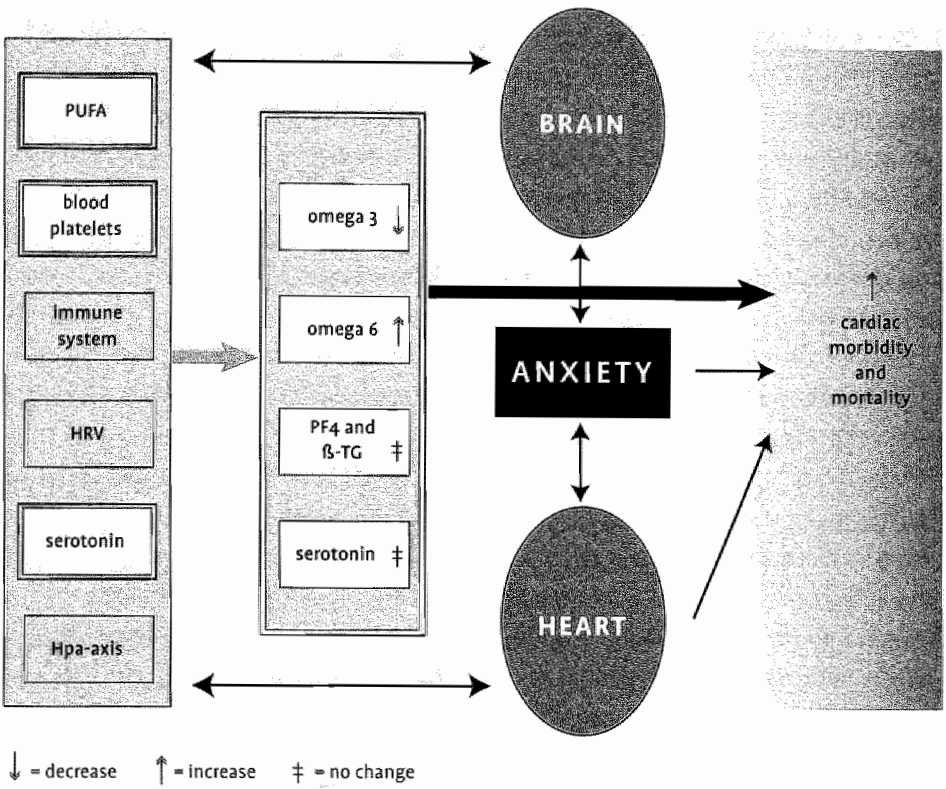
Biological mechanisms which may play a role are increased activity of the sympathetic nervous system, diminished parasympathetic activity, alterations in coagulation and fibrinolysis, polyunsaturated fatty acids (PUFA) and HPA-axis activation [1, 32-35, 37-40].

In our proposed pathophysiological model (figure 1), several biological pathways can play a role as mechanism for increased cardiac morbidity and mortality in anxiety. Of these pathways, blood platelet function, PUFA's and serotonin were investigated in this thesis.

Blood platelet activation was measured using Beta-Thromboglobulin (ß-TG), Platelet Factor 4 (PF4) and soluble CD40 Ligand (sCD40L). We first studied blood platelet activation using PF4 and ß-TG in post-MI patients with and without depression (chapter 8) and found an increased value of PF4 and a trend for increased values of ß-TG in the depressed group. In NCCP-patients with and without PD, we found no differences in these biomarkers between controls and patients (chapter 9). This was contrary to our hypothesis. It seems that blood platelet activation does not play a major role in the relationship between anxiety and increased cardiac morbidity and mortality. Also serotonin levels were not different between controls and patients (chapter 9).

In cardiology, PUFA's play an important role in arrhythmias. Literature has shown that omega 3 PUFA levels are decreased in depressed patients [40]. As depression and anxiety are highly co-occurrent and have a common biological mechanism, we investigated PUFA's

FIGURE 1 | Biological links between anxiety, brain and heart



in our PD driven NCCP-population. Omega 3 levels were decreased in patients, while omega 6 levels were increased in patients compared to controls. This fitted with our hypothesis. We concluded that PUFA's may play a major role in the above-mentioned link between cardiology and psychiatry.

The other biological substances mentioned in figure 1 were not investigated for this thesis. However, we have collected immunologic data in our patient population, and these results will be reported later. HPA-axis function and HRV were not subjects of this thesis either.

Anxiety and cardiac arrhythmias

The relationship between anxiety and cardiac arrhythmias was further investigated in a subpopulation of cardiac patients. During the study period, the awareness of psychopa-

thology in another cardiac population was increasing. These were patients with an Implantable Cardioverter Defibrillator (ICD). Chapter 4 describes a pilot study in which we treated 5 patients with frequent ICD shocks and suffering from PD, depression and agoraphobia, with paroxetine and a behaviour program. We evaluated their heart rhythm with holter registrations. Patients improved markedly as far as psychological and psychiatric complaints were concerned. But of equal importance, the number of ventricular arrhythmias decreased without changing their cardiac medication. During a follow up period of 6 months, in 4 out of 5 patients no ICD-event was registered [41]. These findings support the clinical experience that increased sympathetic drive is related to severe arrhythmias. Treatment of anxiety and depression leads to a reduction of arrhythmias. The exact mechanism or link can only be evaluated in a prospective study. Our pilot study in ICD patients is still continuing and the number of treated patients increasing. Further results will be reported later. This could bring important information to optimize treatment of ICD patients.

Diagnosing PD in a cardiac setting

As indicated earlier, PD driven NCCP is a large problem for the cardiologist. An easy diagnostic instrument which can be used in daily cardiological practice was sought. For this purpose, the HADS was validated for this specific population (chapter 5). When used as screening instrument, we found that a score > 8 on the anxiety subscale had a sensitivity of 88% and a specificity of 64%. For the depression subscale, the cut-off value of > 4 leads to a sensitivity of 88% and specificity of 57%. This implies that the HADS is a sensitive screening instrument for patients with PD-driven NCCP [31]. Application of the HADS in daily cardiological practice (it is an easily applicable instrument) in a FHA setting as well as other cardiac settings, will lead to more adequate referral to a psychiatry outpatient clinic or psychiatric consultation. Such an intervention could help to prevent frequent utilization of health care resources, improve quality of life and probably also cardiac prognosis. A high score on the HADS is not limited to patients without cardiac problems, but is in our experience equally distributed amongst patients with and without a previous cardiac history [31]. One has to realize that patients can have several diagnoses at the same time; the comorbidity between somatic and psychiatric diagnoses is high. A large study of community respondents found that people suffering from one of eight medical disorders had a 41% increase in the relative risk of having any recent psychiatric disorder compared to people without chronic medical conditions [42].

As there is a need for a validated diagnostic instrument to identify PD in patients presenting with NCCP or palpitations [6], we studied the value of the 35% CO_2 challenge test

as a diagnostic tool (chapter 7). In psychiatry, the 35% CO_2 challenge test is a validated instrument for diagnosing PD [43-47]. It is based on the experiments by Gorman in 1984 who investigated the role of forced hyperventilation to induce anxiety. As a control setting, they used 5% CO_2 inhalation, and it appeared that more panic attacks occurred in the control group than in the study sample [48]. At the same time, Griez and Van den Hout used a single breath of 35% CO_2 to trigger anxiety in patients diagnosed with an anxiety disorder [46]. Later, this test has been validated for different types of anxiety disorders, and appears to be a good instrument [48].

It is still not totally clear why carbon dioxide provokes panic. Several biological substances have been tested in panic provocation studies. Substances which are able to provoke panic are for instance lactate, CO_2 and cholecystokinin (CCK)[49, 50]. One of the leading hypotheses is formulated by Klein in 1993 ('False suffocation alarm theory') [45]. An (acute) excess of CO_2 may trigger an inborn suffocation alarm. This leads to acute distress, breathlessness and flight reaction. Panic attacks are thought to be 'false suffocation alarms' in sensitive patients due to a dysregulation of a hypersensitive suffocation detector.

We studied the CO_2 challenge test as a diagnostic instrument in 30 patients with NCCP scoring ≥ 8 on both anxiety and depression subscale of the HADS and subsequently diagnosed with PD and/or depression, and in 24 NCCP patients scoring < 8 without a psychiatric diagnosis. The specificity of the CO_2 challenge test was 87.5% and the sensitivity 63.3%. The positive predictive value was 79.2% and the negative predictive value was 66.3%. There were no clinically relevant or significant electrocardiographic changes during the CO_2 challenge. We therefore concluded that the CO_2 challenge test triggers NCCP specifically in patients presenting with PD and/or depression driven NCCP. The test is safe and easy to administer and should follow the HADS screening.

In order to evaluate a possible vulnerability factor for psychopathology in this group, we studied the prevalence of Type D personality. Type D personality, which is characterized by negative affect and social inhibition, worsens cardiac prognosis. We were interested in the role of Type D personality in patients presenting with PD driven NCCP or palpitations. We examined whether cardiac history or Type D personality is independently associated with PD and/or depression driven NCCP (chapter 6). In the HADS positive group (patients scoring ≥ 8 (N=304)), 89% had a diagnosis of PD and/or depression; 49% had a Type D personality. In the HADS negative group (N=106), only 8% had PD and/or depression and 7% had a Type D personality (p<0,0001). Younger age, male sex and Type D personality were independently associated with increased risk of single or multiple psychiatric diagnoses.

Previous cardiac history, however, was not associated with psychiatric diagnosis. This implies that the assumption that (as one would instinctively expect) a previous cardiac history leads to anxiety or depression is not correct.

The development of psychiatric complaints or a diagnosis such as PD and/or depression is a multifactorial process influenced by several factors. Stressful life events, early life events during childhood and adolescence, as well as maternal overprotection, and personality factors play a role in the development [2]. Genetic factors are also implicated in anxiety [3].

Conclusion and recommendations

Panic disorder driven NCCP is a common problem in daily cardiological practice. It often remains unrecognized, due to the fact that patients report mainly somatic symptoms. This fits with the concept of NFPD: panic attacks without fear. The consequences are a large use of health care resources, economic costs due to loss of working days and unemployment, impaired quality of life and worsened cardiac prognosis due to increased cardiac morbidity and mortality. Of the biological substances that play a role in this increased risk, PUFA's seem to be more important than blood platelet activation.

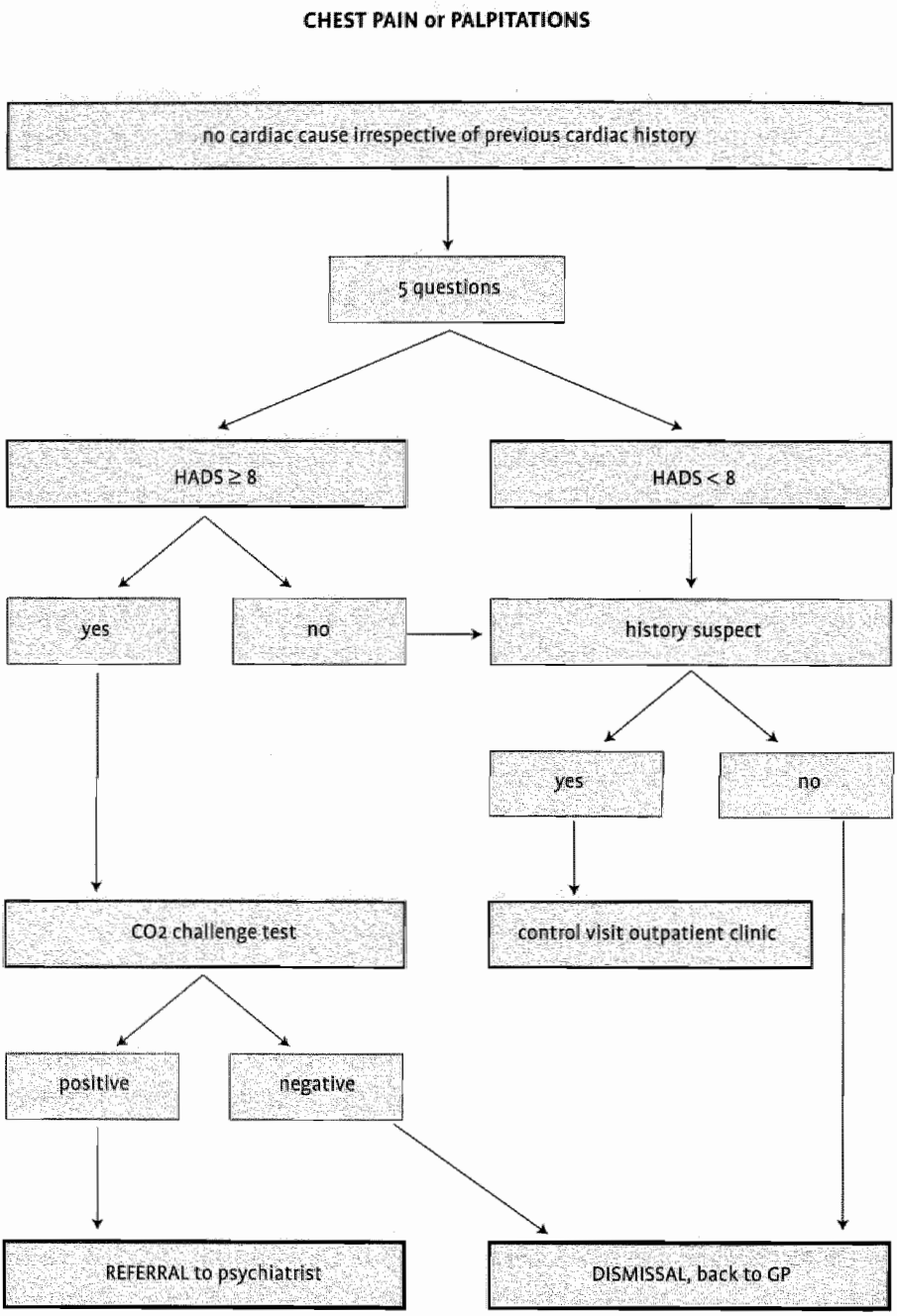
The HADS is a short lasting and simple self-questionnaire with high sensitivity and should be used as a screening instrument. This can be followed by the diagnostic CO_2 challenge test.

A proposal for a practical flow chart for patients presenting with NCCP is depicted in figure 2. First, history taking is essential. Five helpful questions for the cardiologist are:

1. Are there other symptoms of a panic attack present apart from the chest pain?
2. Is there a previous psychiatric history or a family history of psychiatric disorders?
3. Have there been recent stressfull life experiences?
4. Does the chest pain lead to avoidance behaviour?
5. Are there other somatic symptoms present, which may be due to depression, such as tiredness, decreased appetite, sleep disturbances, irritability?

At first sight, asking these questions (which are merely based on experience) does not seem to be the cardiologist's job. However, it is the duty of every doctor (and cardiologist) to treat a patient as good as possible. When a cardiologist discovers for instance diabetes mellitus in a patient, a referral to an internal medicine department is arranged. When a patient suffers from complaints without a somatic cause, however, the cardiologist often dodges the arising situation. But it should be considered a challenge to evaluate the cause

FIGURE 2 | **Flow chart for non cardiac chest pain management**



of the chest pain, and several minutes of good history taking can lead to a correct referral with all its positive consequences. After history taking, suggesting the possibility of NCCP, the patient should fill out a HADS. This takes 5 minutes at most, including calculating the score. If patients have a suspect history and a score > 8 on the HADS anxiety subscale and/or > 4 on the HADS depression subscale, they should be referred for a CO_2 challenge test. When positive, the likelihood of PD is very large. The cardiologist can reassure the patient that despite the fact that he/she experiences chest pain during the test, the ECG shows no abnormalities. This can also help to motivate the patient for psychological or psychiatric treatment, as his/her complaints could be provoked without cardiac consequences. Following this, patients should be referred to a psychiatrist for further diagnosis and treatment.

Future directions

As stated earlier, immunologic data have been collected in these patients a well as in controls. The influence of cytokines should be evaluated as another possible biological link between increased cardiac morbidity as well as mortality and psychiatric disorders. As omega 3 PUFA's are now available in oral form (for secondary prevention after a myocardial infarction), it can be investigated whether treatment with PUFA's leads to a decrease of psychological and psychiatric symptoms in PD and/or depression driven NCCP.

As far as psychiatric treatment for PD and/or depression in our patient population is concerned, it should be evaluated whether effective psychiatric treatment with psychoeducation and/or a selective serotonin reuptake inhibitor leads to a decrease or disappearance of chest pain and/or palpitations. We recently finished a randomised double blind, placebo and care-as-usual controlled study with sertraline. We also collected data on quality of life and health care costs in these groups. Results are currently being analysed and will be reported later. It is important to perform follow-up studies to evaluate cardiac end points such as cardiac morbidity and mortality in this specific patient group.

Lessons from PD driven NCCP should be used to investigate other cardiac populations such as ICD patients and patients with heart failure.

Finally, it seems necessary to include availability of psychiatric/psychological screening in routine cardiac practice. The heart-brain axis is often neglected but seems highly relevant in this vulnerable patient population. When heart and brain are considered as being organs abiding the same laws when ill, than nobody should be afraid of chest pain, not the patient, nor the cardiologist or psychiatrist.

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Summary

The present thesis is a first attempt to map the problem of non cardiac chest pain (NCCP) in daily cardiac practice from the point of view of a cardiologist. Studies were done to assess the incidence and the value of diagnostic tools, others to find possible biological indicators. The thesis is therefore divided into three parts, each consisting of three chapters:

Part A discusses general issues on panic disorder, NCCP and cardiology. Part B focusses on diagnostic issues, and Part C is dedicated to some biological issues.

The introduction (prologue) gives a more elaborate outline of the contents of the thesis, whereas the epilogue puts the findings of the presented studies into perspective, stressing the magnitude of the problem and its consequences.

PART A | *General issues*

Chapter 2

Chapter 2 presents a review of literature on the subject of NCCP and the role of psychiatry. As early as 1871, the 'Irritable Heart syndrome' was introduced. This was one in a long list of names for patients suffering from chest pain without a clear cause. Terms as 'folie cardiaque' suggested an early link between cardiology and psychiatry. Panic disorder (PD) driven chest pain is a major challenge for the cardiologist, as well as the psychiatrist. Unfortunately however, a large group of clinicians is not aware of the fact that affective disorders such as PD and depression can present mainly with somatic complaints and may lead to cardiac morbidity and even increased mortality. Moreover, patients are often not reassured by the fact that the cardiologist did not find any cardiac abnormality. They keep coming back and their health care consumption is high with a worsened quality of life. The economic impact of these complaints is also underestimated.

Chapter 3

To evaluate the magnitude of the problem in a Dutch First Heart Aid (FHA), we performed a pilot study. During 3 months, we studied all patients presenting to the FHA but not admitted to the hospital. All these patients received a Hospital Anxiety and Depression Scale (HADS). When patients scored above the cut-off value of 8 on either subscale (anxiety or depression), their presentation to the FHA was checked. If they presented with chest pain or palpitations and their dismissal diagnosis was 'non cardiac chest pain' or 'no cardiac abnormality', patients were invited for a structured psychiatric interview. Of this latter group, 83% was diagnosed with PD and/or depression. In the FHA the recognition of psychiatric symptoms was very low: in 13% of the cases the attending FHA physician diagnosed 'hyperventilation'. However, probably due to the fact that the cardiologists were aware of the study, the score of 13% recognition was higher than the 2% known from the literature. These findings prompted a larger study, to establish diagnostic methods to recognize this specific patient population.

Chapter 4

The increasing awareness of psychopathology in other cardiac populations was reason to focus on patients with an Implantable Cardioverter Defibrillator (ICD). Chapter 4 describes a pilot study in which we treated 5 patients with frequent ICD shocks and suffering from PD, depression or agoraphobia, with paroxetine and a behaviour program. We evaluated their heart rhythm with frequent 24-hour registrations. Patients not only improved markedly on psychological and psychiatric complaints, but also the number of ventricular arrhythmias decreased without changing their cardiac medication. After a follow up period of 6 months, in 4 out of 5 patients no ICD-event was registered. These findings support the clinical experience that increased sympathetic drive may promote the occurrence of severe arrhythmias. Treatment of anxiety and depression led to an improvement in arrhythmias in this specific (small) group.

PART B | *Diagnostic issues*

Chapter 5

The search for an easy diagnostic instrument for daily cardiological practice focussed primarily on the Hospital Anxiety and Depression Scale (HADS). We performed a study to evaluate the validity of HADS in a population with cardiac complaints. We concluded that

it is an easily applicable and reliable instrument. When used as screening instrument, a score >8 on the anxiety subscale has a sensitivity of 88% and a specificity of 64%. For the depression subscale, the cut-off value of >4 leads to a sensitivity of 88% and specificity of 57%.

This implies that the HADS is a sensitive screening instrument for patients with NCCP. Application of the HADS in daily cardiological practice, both in FHA settings and outpatient or clinical settings, could lead to a much more adequate referral to a psychiatry outpatient clinic or psychiatric consultation.

Chapter 6

In order to assess the vulnerability for psychopathology in our population, we studied the prevalence of Type D personality. Type D personality is characterized by negative affect and social inhibition. Knowing that Type D personality worsens cardiac prognosis, our interest arose in its role in patients presenting with NCCP or palpitations. We examined whether cardiac history or Type D personality is independently associated with PD and/or depression driven NCCP. In the HADS positive group (patients scoring ≥ 8) (N=304)), 89% had a diagnosis of PD and/or depression and 49% had a Type D personality. In the HADS negative group (N=106), only 8% had PD and/or depression and 7% had a Type D personality (p<0,0001). Younger age, male sex and Type D personality were independently associated with increased risk of single or multiple psychiatric diagnoses. Previous cardiac history, however, was not associated with psychiatric diagnosis.

Chapter 7

In chapter 7 we studied the value of the 35% CO_2 challenge test. In psychiatry, this is a well-known and validated test to help diagnose PD. However, no data were known on patients presenting with panic disorder driven NCCP.

We studied the CO_2 challenge test as a diagnostic instrument in 30 patients with NCCP scoring ≥ 8 on both anxiety or depression subscale of the 14-items HADS and subsequently diagnosed with PD and/or depression, and in 24 patients scoring < 8 without a psychiatric diagnosis. The specificity of the CO_2 challenge test was 87.5% and the sensitivity 63.3%. The positive predictive value was 79.2% and the negative predictive value was 66.3%. There were no clinically relevant or significant electrocardiographic changes during the CO_2 challenge. It was concluded that the CO_2 challenge test triggers NCCP specifically in patients presenting with NCCP and diagnosed with PD and/or depression. The test is safe and easy to administer and should follow the HADS screening. Moreover, it appeared

to be a useful instrument for the cardiologist as well as the patient to overcome any possible hesitations on the non cardiac cause of the complaints.

PART C | *Biological issues*

Chapter 8

This chapter covers an early study on blood platelet function in 12 patients with and 12 patients without a depressive disorder after their first myocardial infarction (MI). Patients were matched for age, gender and size of MI. Blood platelet function was evaluated using Beta-thromboglobulin (ß-TG) and Platelet Factor 4 (PF4). These substances are released by blood platelets once activated. It was found that PF4 was increased in the depressed group. ß-TG was also increased but not statistically significant compared to the non-depressed patients.

Chapter 9

Do blood platelets also play a role in PD and/or depression driven NCCP? In order to answer that question we studied ß-TG, PF4, sCD40L and serotonin.

Anxiety and depression are prognostic indicators for increased morbidity and mortality in cardiac patients. The link between this could be blood platelets. Activated blood platelets release several substances such as ß-TG, PF4, sCD40L and serotonin. Increased levels of serotonin are associated with coronary artery disease (CAD) and occurrence of cardiac events. Serotonin metabolism is one of the key factors in the pathophysiology of depression and anxiety. We hypothesized that (i) PF4, ß-TG and sCD40L are higher in patients and that (ii) 5HT levels are not different between controls and patients. Patients with NCCP diagnosed with PD and/or depression (n=49) were compared with a control population consisting of subjects with NCCP without a psychiatric diagnosis (n=18). There were no statistically significant differences between both groups as far as ß-TG, PF4, serotonin, and sCD40L is concerned. It was concluded that blood platelets do not seem to play a major role in PD and/or depression driven NCCP.

Chapter 10

Anxiety has been proven to be an independent risk factor for cardiovascular death, especially sudden cardiac death. A decrease in omega-3 polyunsaturated fatty acids (PUFA's) has been associated with cardiac mortality and affective dysregulation. Therefore, one of

the mechanisms of PD related mortality-increase might be a change in PUFA levels. We hypothesised that omega 3 PUFA levels are decreased and omega 6 PUFA levels are increased in patients with PD and/or depression driven NCCP.

PUFA status was measured in phospholipids of twenty patients with NCCP without a psychiatric diagnosis and of 54 patients suffering from PD and/or depression driven NCCP. The hypothesis was confirmed: we found decreased levels of omega 3 PUFA's, while omega 6, omega 6/3 ratios and AA/EPA ratio were increased in the patient group. It was concluded that NCCP patients, suffering from PD and/or depression, have lower omega 3 PUFA levels and elevated omega 6 PUFA levels. These findings may play a role in the relationship between anxiety and sudden cardiac death.

EPILOGUE

Chapter 11

The epilogue summarizes the main conclusions of this thesis. An attempt is made to implement the findings of this thesis into a practical flow chart for the cardiologist. Also a model on the pathophysiology between increased morbidity and mortality is presented. Finally, 5 questions are suggested to be used in daily practice to help the cardiologist to identify this specific (and large!) group of patients.

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Samenvatting

Dit proefschrift is een eerste internationale poging om het probleem van niet-cardiale pijn op de borst (non cardiac chest pain, NCCP) in de dagelijkse cardiologische praktijk in kaart te brengen vanuit het oogpunt van een cardioloog. De beschreven studies werden gedaan om het vóórkomen van het probleem nader te bestuderen, de waarde van diagnostische hulpmiddelen te onderzoeken en biologische stoffen te vinden die mogelijk een rol spelen in de relatie tussen hartklachten en psychiatrische klachten. Derhalve is dit proefschrift verdeeld in 3 delen, elk bestaande uit 3 hoofdstukken:

Deel A beschrijft in het algemeen paniekstoornis, niet-cardiale pijn op de borst en de relatie met cardiologie. Deel B richt zich met name op diagnostische instrumenten, en deel C is gewijd aan biologische onderwerpen. De introductie (prologue) die hieraan vooraf gaat, geeft meer uitleg over de onderwerpen van het proefschrift, terwijl de algemene discussie (epilogue) de bevindingen van het proefschrift in een breder perspectief plaatst.

DEEL A | *Algemene aspecten*

Hoofdstuk 2

Hoofdstuk 2 geeft een literatuuroverzicht van NCCP en de rol van de psychiatrie. Reeds in 1871 werd de term *Irritable Heart syndrome* geïntroduceerd. Dit was een van de eerste benamingen uit een lange reeks voor pijn op de borst zonder duidelijke (cardiale) oorzaak. Benamingen als *folie cardiaque* suggereerden al vroeg een verband tussen cardiologie en psychiatrie.

Pijn op de borst die veroorzaakt wordt door een Paniekstoornis (PS) is een grote uitdaging voor zowel de cardioloog als de psychiater. Helaas is een grote groep clinici niet op de hoogte van het feit dat affectieve stoornissen zoals een PS of depressie zich soms voor-

namelijk met lichamelijke klachten kunnen openbaren. Ook is het nog vrij onbekend dat depressie en PS tot een verhoogde kans op cardiale aandoeningen en sterfte kan leiden. Bovendien zijn de patiënten zelf vaak alles behalve gerustgesteld door de mededeling van de cardioloog dat er "met het hart niets aan de hand is". Zij blijven klachten houden en dientengevolge naar het ziekenhuis terugkomen. Dit mondt uit in een hoge consumptie van gezondheidszorgvoorzieningen en een verminderde kwaliteit van leven. Ook de economische consequenties worden over het algemeen onderschat.

Hoofdstuk 3

Om inzicht te krijgen in de omvang van het probleem op een Nederlandse Eerste Hart Hulp (EHH), is een proefstudie uitgevoerd. Gedurende 3 maanden werden alle patiënten gevolgd die zich op deze EHH meldden en niet in het ziekenhuis werden opgenomen. Al deze patiënten ontvingen een Hospital Anxiety and Depression Scale (HADS). Indien patiënten boven de grenswaarde van 8 scoorden op een van beide subschalen (angst en/of depressie), werden de gegevens van het EHH-bezoek onderzocht. Indien de aanmeldklacht 'pijn op de borst' of 'hartkloppingen' was, en de ontslagdiagnose 'niet-cardiale pijn op de borst' of 'geen cardiale afwijkingen', werden patiënten uitgenodigd voor een gestructureerd psychiatrisch interview. Van deze laatste groep bleek 83% de diagnose 'paniekstoornis' en/of 'depressie' te hebben.

De herkenning van psychiatrische symptomen op de EHH was erg laag: in slechts 13% van de gevallen was er door de dienstdoende arts 'hyperventilatie' gediagnosticeerd. Daar komt bij dat, waarschijnlijk door het feit dat men op de hoogte was van de lopende studie, het herkenningspercentage van 13% hoger was dan de 2% die uit de literatuur bekend is. Deze bevindingen hebben direct geleid tot een grotere studie, waarin diagnostische methoden getest konden worden om uiteindelijk deze specifieke patiëntenpopulatie te kunnen herkennen.

Hoofdstuk 4

Het toenemende besef van psychopathologie bij andere cardiale populaties leidde tot gerichte interesse voor patiënten met een geïmplanteerde defibrillator (Implantable Cardioverter Defibrillator (ICD)). Hoofdstuk 4 beschrijft een proefstudie waarin we 5 patiënten met frequente ICD-shocks en PS en/of agorafobie alsmede depressie, behandelden met paroxetine en een gedragsprogramma. Tijdens de behandeling werd het hartritme geëvalueerd door middel van frequente 24-uurs-registraties. Patiënten bleken niet alleen psy-

chologisch en psychiatrisch flink te verbeteren, maar ook daalde het aantal kamerhartritmestoornissen, wardoor er minder shocks optraden; dit alles zonder de cardiale medicatie te veranderen. Na een follow-up-periode van 6 maanden, bleek er bij 4 van de 5 patiënten geen ICD-shock meer te zijn opgetreden. Deze bevindingen onderstrepen de klinische ervaring dat een toegenomen sympathicus-prikkeling het optreden van ernstige hartritmestoornissen mede beïnvloedt. In deze specifieke kleine groep leidde behandeling van angst en depressie tot een afname van hartritmestoornissen.

DEEL B | *Diagnostische aspecten*

Hoofdstuk 5

De zoektocht naar een makkelijk toepasbaar (psychiatrisch) diagnostisch instrument voor de dagelijkse cardiologische praktijk, richtte zich primair op de Hospital Anxiety and Depression Scale (HADS). Om de validiteit van de HADS te onderzoeken voerden wij een studie uit bij een populatie die zich meldde op de EHH met hartklachten. Wij konden concluderen dat de HADS een makkelijk toepasbaar en betrouwbaar instrument is bij deze specifieke groep. Indien gebruikt als screenings-instrument, heeft een score >8 op de angst-subschaal een sensitiviteit van 88% en een specificiteit van 64%. Wat betreft de depressie-subschaal heeft een grenswaarde >4 een sensitiviteit van 88% en een specificiteit van 57%.

Dit impliceert dat de HADS een gevoelig screenings-instrument is voor patiënten met niet-cardiale pijn op de borst. Toepassing van de HADS in de dagelijkse cardiologische praktijk, zowel op een EHH, in de kliniek als poliklinisch, kan leiden tot een meer adequaat verwijzingspatroon naar een polikliniek psychiatrie of consultatieve psychiatrie.

Hoofdstuk 6

Om de kwetsbaarheid voor psychopathologie te achterhalen, hebben we gekeken naar de prevalentie van de Type D-persoonlijkheid binnen onze onderzoekspopulatie. Type D-persoonlijkheid wordt gekarakteriseerd door negatief affect en sociale inhibitie. In de literatuur is aangetoond dat Type D-persoonlijkheid de cardiale prognose verslechtert. Welke rol die Type D-persoonlijkheid speelt in patiënten die zich presenteren met NCCP of hartkloppingen was echter nog niet eerder onderzocht. Wij bekeken of een cardiale voorgeschiedenis of Type D-persoonlijkheid onafhankelijk geassocieerd is met PS- en/of depressie-gerelateerde NCCP. In de HADS-positieve groep (patiënten met een score ≥ 8 (N=304)),

had 39% de diagnose PS en/of depressie en 49% een Type D-persoonlijkheid. In de HADS-negatieve groep (N=106), had slechts 8% PS en/of depressie en 7% een Type D-persoonlijkheid ($p<0.0001$). Jongere leeftijd, mannelijk geslacht en Type D-persoonlijkheid waren onafhankelijk geassocieerd met een toegenomen risico op een enkele of dubbele psychiatrische diagnose. Het hebben van een cardiale voorgeschiedenis bleek niet geassocieerd te zijn met een psychiatrische diagnose.

Hoofdstuk 7

In Hoofdstuk 7 is de diagnostische waarde van de 35%CO_2-provocatietest beschreven. In de (experimentele) psychiatrie is dit een bekende en goed gevalideerde test om PS te diagnosticeren. Er zijn echter geen data bekend bij patiënten met PS-gerelateerde NCCP.

Wij bestudeerden de CO_2-provocatietest als diagnostisch instrument bij 30 patiënten met NCCP die een score hadden van ≥ 8 op de angst- danwel depressie-subschaal van de HADS (14-items) en vervolgens waren gediagnosticeerd met PS en/of depressie, alsmede bij 24 patiënten die < 8 scoorden zonder psychiatrische diagnose. De specificiteit van de CO_2-provocatietest was 87,5% en de sensitiviteit 63,3%. De positief voorspellende waarde bedroeg 79,2%, de negatief voorspellende waarde 66,3%. Er traden geen klinisch relevante of significante electrocardiografische veranderingen op tijdens de CO_2-test.

Wij concludeerden dat de 35%CO_2-provocatietest NCCP kan uitlokken in deze specifieke patiëntengroep. De test is veilig en makkelijk toepasbaar, en zou derhalve gebruikt moeten worden als aanvulling op de HADS-screening. Bovendien lijkt het een bruikbaar instrument te zijn voor zowel de cardioloog als de patiënt om twijfels over de niet-cardiale oorzaak van de pijn op de borst weg te nemen.

DEEL C | *Biologische aspecten*

Hoofdstuk 8

Dit hoofdstuk beschrijft een eerdere studie naar bloedplaatjesfunctie bij 12 patiënten met en 12 patiënten zonder depressie na een eerste hartinfarct. Patiënten waren 'gematched' wat betreft leeftijd, geslacht en grootte van het hartinfarct. De bloedplaatjesfunctie werd geëvalueerd door te kijken naar Beta-thromboglobulin (ß-TG) en Platelet Factor 4 (PF4). Deze stoffen komen vrij uit geactiveerde bloedplaatjes. Wij vonden dat PF4 toegenomen is in de depressieve groep. ß-TG was ook verhoogd ten opzichte van de niet-depressieve groep, maar niet statistisch significant.

Hoofdstuk 9

Spelen bloedplaatjes ook een rol in PS- en/of depressiegerelateerde NCCP? Om deze vraag te beantwoorden onderzochten we ß-TG, PF4, sCD40L en serotonine (5HT) in de NCCP groep.

Angst en depressie zijn prognostische indicatoren voor toegenomen morbiditeit en mortaliteit bij hartpatiënten. Bloedplaatjes zouden hierin de verbindende factor kunnen zijn. Bij activatie van bloedplaatjes komen diverse stoffen vrij, waaronder ß-TG, PF4, sCD40L en serotonine. Een verhoogd serotonineniveau is geassocieerd met coronarialijden en het optreden van cardiale gebeurtenissen. Serotonine-metabolisme is een van de belangrijkste factoren in de pathofysiologie van depressie en angst. Onze hypothese was (i) PF4, ß-TG en sCD40L zijn verhoogd bij patiënten en (ii) de 5HT-waarde verschilt niet tussen patiënten en controles. Patiënten met NCCP en PS en/of depressie (n=49) werden vergeleken met een controle groep bestaande uit patiënten met NCCP zonder een psychiatrische diagnose (n=18). Tussen beide groepen bleken er geen statistisch significante verschillen te zijn wat betreft ß-TG, PF4, serotonine, alsmede sCD40L. Wij concludeerden derhalve dat bloedplaatjes geen belangrijke rol lijken te spelen bij PS- en/of depressie-gerelateerde NCCP.

Hoofdstuk 10

Angst is een bewezen onafhankelijke risicofactor voor cardiovasculaire dood, met name plotse hartdood. Een afgenomen hoeveelheid omega-3 vetzuren (polyunsaturated fatty acids (PUFA's)) is geassocieerd met cardiale mortaliteit, alsmede affectieve disregulatie. Derhalve zou een van de mogelijke mechanismen van PS-gerelateerde mortaliteit een verandering in PUFA's kunnen zijn. Onze hypothese was dat omega-3 PUFA's verlaagd zijn en omega-6 PUFA's verhoogd bij patiënten met PS- en/of depressiegerelateerde NCCP.

Bij twintig patiënten met NCCP zonder psychiatrische diagnose en 54 patiënten met PS- en/of depressiegerelateerde NCCP werd de PUFA-status gemeten in fosfolipiden. Onze hypothese werd bevestigd: de omega-3 PUFA's waren verlaagd, terwijl omega-6, omega-6/3 ratio's en de AA/EPA-ratio verhoogd waren in de patiëntengroep. De conclusie was dat NCCP-patiënten met PS en/of depressie, lagere omega-3 PUFA's hebben en verhoogde omega-6 PUFA's. Deze bevindingen kunnen een rol spelen in de relatie tussen angst en plotse hartdood, die echter in ons huidige onderzoek nog niet bestudeerd zijn.

EPILOOG

Hoofdstuk 11

De epiloog vat de belangrijkste conclusies van dit proefschrift samen. Er wordt een poging gedaan om alle bevindingen te implementeren in een praktisch stroomschema dat door de cardioloog gebruikt kan worden. Ook wordt er een model getoond betreffende de pathofysiologische links tussen angst, depressie en de toegenomen (cardiale) morbiditeit en mortaliteit. Tot slot worden er 5 vragen voorgesteld die de cardioloog kan gebruiken in de dagelijkse praktijk als hulp bij het identificeren van deze specifieke (en grote!) groep patiënten.

dankwoord

publications

curriculum vitae

Dankwoord

Hoe kan men een dankwoord nog origineel beginnen... Vele voorgangers hebben dit dankwoord altijd als laatste klus geschreven. Omdat je hier altijd lang over loopt na te denken, niemand wil vergeten, iedereen alle verdiende lof en eer wil doen toekomen, zo ook ik. Hoe ben ik ooit tot promoveren gekomen? Soms doen zich plotseling kansen voor die je op dat moment moet aangrijpen. Gaandeweg het promotie-onderzoek heb ook ik herhaaldelijk gedacht "waar ben ik aan begonnen....". Het is niet altijd een makkelijke opgave geweest om naast klinische werkzaamheden en ziekte toch alles binnen redelijke termijnen af te ronden, maar zoals mijn sterrenbeeld (stier) doet vermoeden, bleef ik gewoon doorgaan, en het resultaat ligt nu voor u.

Binnen de medische wereld is de heersende opinie over vakgebieden grotendeels gebaseerd op Descartes idee dat lichaam en geest gescheiden entiteiten zijn. Dat deze veronderstelling ter discussie gesteld zou moeten worden, toont de gestaag groeiende berg publicaties aan waarin de wisselwerking tussen lichaam en geest een rol speelt. De indeling van specialismen (somatiek vs psychiatrie) heeft tot gevolg dat veel patiënten tussen wal en schip belanden. De nieuwe multidisciplinaire aanpak waar dit proefschrift van getuigt is een voorzichtig begin in het doorbreken van de ingesleten patronen. Dat er ondanks uitgebreide pogingen een aantal hoofdstukken nog niet gepubliceerd is, laat zien dat de Cardiopsychiatrie nog steeds een moeilijk onderwerp is. Pionieren is niet makkelijk, maar wel boeiend en uitdagend.

Maar dan nu de dankwoorden. Ik ben van mening dat ik als eerste alle patiënten die op enigerlei wijze hebben meegewerkt aan dit proefschrift zeer hartelijk moet bedanken. Zonder patiëntenmedewerking geen patiëntgebonden onderzoek!

Hoe ben ik ooit op dit Cardiopsychiatrie-pad terecht gekomen? Daar heeft mijn eerste promotor, Professor Wellens een beslissende rol in gespeeld. Door zijn regelmatige contacten met Professor Van Praag was hij ervan overtuigd geraakt dat dit een onderwerp was dat binnen de cardiologie aandacht verdiende en potentieel interessant en vernieuwend was.

Hij heeft mij op het station van Adriaan Honig afgezet. Geleidelijk aan is het Cardiopsychiatrie-boemeltje een Intercity geworden.

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Maastricht, mei 2005,
Petra

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  JJMH Strik, A Honig, J van Os, R Lousberg, PMJC Kuijpers, HJJ Wellens, HM van Praag
  -American Psychiatric Association, May 1999
  -Working group Cardiological Centers Netherlands Amsterdam, December 11th 1999, poster
- *Depression following a first myocardial infarction: a prospective study of incidence and relationship with size of infarction*
  JJMH Strik, A Honig, J van Os, PMJC Kuijpers, R Lousberg, HJJ Wellens, HM van Praag
  -Working group Cardiological Centers Netherlands Amsterdam, December 11th 1999, posters
- *Fluoxetine in the treatment of depression and hostility in patients with major depression following first myocardial infarction: a double blind placebo-controlled trial*
  JJMH Strik, A Honig, R Lousberg, AHP Lousberg, EC Cheriex, PMJC Kuijpers, HG Tuynman-Qua, HJJ Wellens, HM van Praag.
  -Working group Cardiological Centers Netherlands Amsterdam, December 11th 1999, poster
- *Size of myocardial infarction (MI) has an inverse relationship with depression after a first MI in the first three months post-MI*
  PMJC Kuijpers, J Strik, A Honig, R Lousberg, FH van der Veen, HM van Praag, HJJ Wellens
  -Euron PhD students day 14-15 September 2000, Maastricht, poster
  -Spring meeting Dutch Society of Cardiology, Den Haag, April 28th 2000, poster
- *Blood platelet functioning in post myocardial infarction patients with a major depression*
  PMJC Kuijpers, A Honig, K Hamulyak, M Maes, HJJ Wellens
  -Dutch Society Psychiatry, Maastricht, March 29-31 2000, poster
  -Spring meeting Dutch Society of Cardiology, Den Haag, April 28th 2000, poster
  -Euron PhD students day 14-15 September 2000, Maastricht, poster
- *Efficacy and safety of fluoxetine in the treatment of patients with major depression following first myocardial infarction: findings from a double-blind placebo-controlled trial.*
  JJMH Strik, A Honig, R Lousberg, AHP Lousberg, EC Cheriex, PMJC Kuijpers, HG Tuynman-Qua, HJJ Wellens, HM van Praag.
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- *Platelet Factor 4 and Beta Thromboglobulin levels in post-myocardial infarction patients having a depressive disorder*
  PMJC Kuijpers, A Honig, K Hamulyak, M Maes, HJJ Wellens
  -Amsterdam Coagulation symposium, AMC Amsterdam, September 15th 2000, lecture and abstract in workshop laboratorium research
- *Cardiovascular side effects of fluoxetine in depressed patients with a first myocardial infarction: findings from a placebo-controlled study.*
  JJMH Strik, A Honig, R Lousberg, A Lousberg, EC Cheriex, H Tuynman-Qua, PMJC Kuijpers, HJJ Wellens, HM van Praag
  -Dutch Society Psychiatry, Maastricht, March 29-31 2000, poster
- *Panic symptoms determine type of health care*
  K Schruers, P Kuijpers, A Honig, E Griez
  -Dutch Society Psychiatry, Rotterdam, April 4-6 2001, poster
  -14th European Health Psychology Society conference. Models of health and illness behaviour, August 16-19 2000, poster
- *The psychiatric and cardiac effects of paroxetine in patients with an implantable cardioverter defibrillator*
  PMJC Kuijpers, A Honig, C van Velden-Hendriks, R Lousberg, HJJ Wellens
  -14th European Health Psychology Society conference. Models of health and illness behaviour, August 16-19 2000, poster

- *The effects of treatment with sertraline for panic disorder and/or depression driven chest pain and/or palpitations: a treatment protocol.*
  PMJC Kuijpers, A Honig, IGA Foolen, D Brunenberg, CD Dirksen, R Lousberg, M Maes, HJJ Wellens
  -14th European Health Psychology Society conference. Models of health and illness behaviour, August 16-19 2000, poster
- *Effect of treatment of panic disorder in patients with frequent ICD-discharges*
  PMJC Kuijpers, A Honig, HJJ Wellens
  -Spring meeting, Scheveningen, April 29th 2002, poster, abstract
  -Netherlands Heart Journal 2002;10 (suppl 1):9-10
- *The validity and clinical usefullness of the Hospital Anxiety and Depression Scale in patients with noncardiac chest pain.*
  PMJC Kuijpers, J Denollet, R Lousberg, HJJ Wellens, H Crijns, A Honig
  -Dutch Society of Cardiology Ermelo, October 25th 2002, poster, abstract
  -American Psychiatric Association, San Francisco, May 2003
- *Study design of "The effects of treatment with sertraline or cognitive behavioural therapy for panic disorder and/or depression driven chest pain"*
  PMJC Kuijpers, GA van Zijderveld, D Brunenberg, CD Dirksen, H Crijns, R van Dyck, HJJ Wellens, A Honig
  -Dutch Society of Cardiology Ermelo, October 25th 2002, poster, abstract
- *Value of the 35% CO2 challenge test for diagnosing panic disorder in patients presenting with noncardiac chest pain.*
  PMJC Kuijpers, H. Crijns, E Griez et al
  -Dutch Society of Cardiology Ermelo, October 23-24 2003, poster, abstract
- *Cost effectiveness of pharmacological treatment versus care as usual for panic disorder and/or depression driven chest pain: preliminary results of unblinded data.*
  Brunenberg D, Dirksen C, Kuijpers P, Honig A
  -International Society for Pharmacoeconomic and outcomes research, 6th Annual European Congress, Barcelona, November 9-11 2003
- *Relationship between efficacy, quality of life and side-effects of psycho-education plus sertraline and psycho-education plus placebo for panic disorder and/or depression driven chest pain*
  D.E.M. Brunenberg, P.M.J.C. Kuijpers, C.D. Dirksen, A. Honig
  -29ste Werkgroep Epidemiologisch Onderzoek Nederland, Leiden, June 10-11 2004, poster
- *Cost-effectiveness of sertraline for panic disorder and/or depression driven chest pain*
  D.E.M. Brunenberg, C.D. Dirksen, P.M.J.C. Kuijpers, A. Honig
  -International Center of Mental Health Policy and Economics, Seventh Workshop on Costs and Assessment in Psychiatry, Venice, March 18-20, 2005

Curriculum vitae

Petra Maria Josephina Catharina Kuijpers werd geboren op 23 april 1964 in Maastricht. Na het behalen van haar VWO-diploma aan het Maastrichtse Jeanne d'Arc Lyceum in 1982, begon zij met de studie Geneeskunde aan de Rijksuniversiteit Limburg (nu Universiteit Maastricht). In 1988 behaalde zij haar artsdiploma, waarna zij als arts-assistent (AGNIO) ging werken op de afdeling Cardiologie van het Academisch Ziekenhuis Maastricht. Een jaar later startte zij met haar opleiding tot cardioloog bij Professor dr. HJJ Wellens.

Zij werkte gedurende twee jaar op de afdeling Interne Geneeskunde van het Maasland Ziekenhuis Sittard, waarna ze de opleiding vervolgde bij de afdeling Cardiologie van het Academisch Ziekenhuis Maastricht en deze aldaar in 1996 afrondde.

Na enige tijd als cardioloog werkzaam te zijn geweest in het St. Jozef Ziekenhuis Kerkrade, begon ze in 1998 aan een bijzonder experiment door zich als cardioloog te verbinden aan de afdeling Psychiatrie van het Academisch Ziekenhuis Maastricht. Hier werkte ze mee aan het opstarten van enkele grote multidisciplinaire studies, waarvan zij uiteindelijk zelf de studie 'Paniekstoornissen en pijn op de borst' voor haar rekening nam, resulterend in dit proefschrift. Daarnaast was zij als cardioloog verbonden aan de pas opgerichte multidisciplinaire afdeling 'MedPsychUnit' van het AZM.

In 2002 behaalde ze het European Certificate in 'Anxiety and Mood Disorders' en in 2003 een Master-titel in 'Affective Neuroscience' bij onder meer Professor dr. EJL Griez.

Momenteel is ze werkzaam voor zowel de afdeling Cardiologie als de afdeling Psychiatrie van het Academisch Ziekenhuis Maastricht met als subspecialisme de 'cardiopsychiatrie'.

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